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(54) Title: IMMUNOSUPPRESSIVE AND TOLEROGENIC MODIFIED LEWIS^C AND LacNAc COMPOUNDS

(57) Abstract

Disclosed are novel Lewis^C and LacNAc analogues, pharmaceutical compositions containing such analogues, methods for their preparation and methods for their use.

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IMMUNOSUPPRESSIVE AND TOLEROGENIC MODIFIED LEWIS^c AND LacNAc COMPOUNDS

BACKGROUND OF THE INVENTION

1. Field of the Invention.

The present invention is directed to Lewis^c-YR and LacNAc-YR analogues, pharmaceutical compositions containing such analogues, methods for their preparation and methods for their use.

2. References

The following references are cited in this application as superscript numbers at the relevant portion of the application:

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All publications and patent applications are herein incorporated by reference in their entirety to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

3. State of the Art

Carbohydrates and/or oligosaccharides are present on a variety of natural and pathological glycoconjugates[1]. Of particular interest are carbohydrates and oligosaccharides containing sialyl and/or fucosyl residues[3]. Such sialyl and/or fucosyl carbohydrates and oligosaccharides are present in a number of products which have been implicated in a wide range of biological phenomena based, in part, on the concept of recognition signals carried by the carbohydrate structures and by their binding to specific ligands.

Specifically, a number of sialylated and sialylated/fucosylated oligosaccharide glycosides have been proposed as mediators of cell adhesion in that they are ligands for selectins (or LEC-CAM's)[4,5,6,7]. Sialylated, fucosylated, and sialylated and fucosylated oligosaccharide structures relating to blood group

determinants having a type I or a type II core structure, including Lewis^X, Lewis^A, sialyl Lewis^X and sialyl Lewis^A, have also been shown by Ippolito et al.[2,13] to possess in vivo immunomodulating and tolerogenic properties in mammals including anti-inflammatory immunomodulating properties.

In regard to the above, the DTH anti-inflammatory immunomodulating properties of Lewis^X and sialyl Lewis^X reported by Ippolito et al.[2,13] demonstrate that the presence of the sialyl residue on sialyl Lewis^X results in enhanced anti-inflammatory activity as compared to Lewis^X and that the presence of a fucosyl group on sialyl Lewis^X results in enhanced anti-inflammatory activity as compared the anti-inflammatory activity of sialyl LacNAc.

Contrarily, oligosaccharide glycosides containing a sialyl group and/or a fucosyl group as well as related compounds are difficult to chemically synthesize in high yield. For example, synthesis of the αNeu5Ac(2→3)βGal disaccharide unit in compounds such as sialyl Lewis^X and sialyl Lewis^A with anomeric specificity for the α(2→3) is known to be difficult. Known chemical methodologies include a multistep synthesis which first generates a blocked αNeu5Ac(2→3)Gal disaccharide having a suitable leaving group at the reducing sugar terminus of the galactose[8,9]. This disaccharide is then reacted with a suitably protected GlcNAc-OR saccharide glycoside and then a suitably protected L-fucose derivative which, after deprotection, provides for the sialyl Lewis^X glycoside [αNeu5Ac(2→3)βGal(1→4)[αFuc(1→3)]-βGlcNAc-OR] or the sialyl Lewis^A glycoside [i.e,

αNeu5Ac(2→3)βGal(1→3)-[αFuc(1→4)]-βGlcNAc-OR] where R is an aglycon of at least one carbon atom.

While it is well known that sialylation and fucosylation can be conducted as part of an overall chemical/enzymatic synthesis[2,9,10] of compounds such as sialyl Lewis^A and sialyl Lewis^X, such processes require compatible sialyltransferases and fucosyltransferases which are not always readily available. For example, the βGal(1→3/4)βGlcNAc α(2→3)sialyltransferase disclosed in the art for sialylating the βGal(1→4)βGlcNAc backbone is currently recovered from rat livers[11].

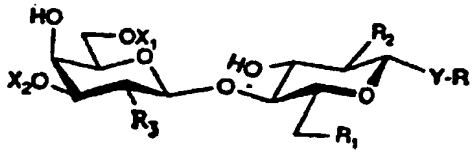
In any event, the inclusion of a sialyl and/or a fucosyl residue on LacNAc-OR and Lewis^C-OR so as to provide for sialyl and/or fucosylated derivatives results in a more complex and costly synthesis.

SUMMARY OF THE INVENTION

The present invention is directed, in part, to the discovery that modified Lewis^C-YR and modified LacNAc-YR compounds having a sulfate, a phosphate or a carboxylate containing group at the 2, 3 and/or 6-positions of the galactose unit possess good immunosuppressive and tolerogenic properties. Moreover, the 3-sulfate Lewis^C-YR compound possesses approximately equivalent immunosuppressive properties as compared to sialyl Lewis^X-YR. This result is particularly surprising insofar as unmodified Lewis^A-YR and sialyl Lewis^A-YR possess inferior immunosuppressive properties as compared to the 3-sulfate of Lewis^C-YR. Additionally, these modified LacNAc-YR and modified Lewis^C-YR compounds do not require formation of an

α(2→3) sialyl residue on the galactose or a fucosyl residue at the 3- or 4-position of the GlcNAc residue in order to impart biological activity. Accordingly, the synthesis of biologically active molecules is simplified and the inclusion of a required sialyl group or a required fucosyl group is avoided. However, in this regard, the optional inclusion of a sialyl group at the 6-position of the galactose having a sulfate, phosphate or $-CHR_{18}COOH$ group at the 2- or 3-position of the galactose is contemplated herein.

Accordingly, in one of its composition aspects, the present invention is directed to compounds of Formula I or II:



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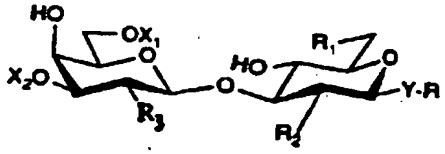


II

where R is selected from the group consisting of hydrogen, a saccharide-OR_{19}, an oligosaccharide-OR_{19} having from 2 to 7 oligosaccharide units, or an aglycon having at least 1 carbon atom where R_{19} is hydrogen or an aglycon of at least one carbon atom;

Y is selected from the group consisting of oxygen, sulfur, and -NH-;

R_1 is selected from the group consisting of hydrogen, $-NH_2$, $-N_3$, $-NHSO_3H$, $-NR_5C(O)R_4$, $-N=C(R_5)_2$,

$-NHCH(R_5)_2$, $-NHR_6$, $-N(R_6)_2$, $-OH$, $-OR_6$, $-S(O)R_6$, $-S(O)_2R_6$ and sulfate,

wherein R_4 is selected from the group consisting of

hydrogen,

alkyl of from 1 to 4 carbon atoms;

$-OR_7$ wherein R_7 is alkyl of from 1 to 4 carbon atoms, or alkyl of from 2 to 4 carbon atoms substituted with a hydroxyl group, and

$-NR_8R_9$ wherein R_8 and R_9 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 4 carbon atoms,

each R_5 is selected from the group consisting of hydrogen and alkyl of from 1 to 4 carbon atoms,

each R_6 is alkyl of from 1 to 4 carbon atoms,

R_2 is selected from the group consisting of hydrogen, $-N_3$, $-NH_2$, $-NHSO_3H$, $-NR_{11}C(O)R_{10}$, $-N=C(R_{11})_2$, $-NHCH(R_{11})_2$, $-NHR_{12}$, $-N(R_{12})_2$, $-OH$ and $-OR_{12}$,

wherein R_{10} is selected from the group consisting of

hydrogen,

alkyl of from 1 to 4 carbon atoms,

$-OR_{13}$ wherein R_{13} is alkyl of from 1 to 4 carbon atoms, or alkyl of from 2 to 4 carbon atoms substituted with a hydroxyl group, and

$-NR_{14}R_{15}$ wherein R_{14} and R_{15} are independently selected from the group consisting of hydrogen and alkyl of from 1 to 4 carbon atoms,

each R_{11} is selected from the group consisting of hydrogen and alkyl of from 1 to 4 carbon atoms;

each R_{12} is alkyl of from 1 to 4 carbon atoms,

R_3 is selected from the group consisting of hydrogen, fluoro, sulfate and hydroxy;

X_1 is selected from the group consisting of hydrogen, sialyl, sulfate, phosphate, and $-CHR_{18}COOH$

where R_{18} is selected from the group consisting of hydrogen, alkyl of from 1 to 7 carbon atoms and -COOH;

X_2 is selected from the group consisting of hydrogen, sulfate, phosphate, and $-CHR_{18}COOH$ where R_{18} is selected from the group consisting of hydrogen, alkyl of from 1 to 7 carbon atoms and -COOH; and pharmaceutically acceptable salts thereof;

and with the proviso that either at least one of X_1 or X_2 is sulfate, phosphate or $-CHR_{18}COOH$ or R_3 is sulfate.

The compounds of Formula I and II are useful in modulating a cell-mediated immune inflammatory response and in particular a cell-mediated immune inflammatory response to an antigen.

The compounds of this invention are particularly useful in reducing antigen induced inflammation in a sensitized mammal. In this regard, when the compounds of Formula I and II are administered to a sensitized mammal in response to an antigen challenge, such administration induces tolerance to later challenges from this same antigen. Preferably, administration of a compound of Formula I or II above is after initiation of the mammal's immune response but at or prior to one-half of the period of time required for the mammal to reach maximal inflammation.

In another of its composition aspects, the present invention is directed to a pharmaceutical composition suitable for administration to a mammal (e.g., human) which comprises a pharmaceutically inert carrier and an effective amount of the compound of

Formula I or Formula II to modulate a cell-mediated immune inflammatory responses in said mammal.

In one of its method aspects, the present invention is directed to a method for modulating a cell-mediated immune inflammatory response in a mammal which method comprises administering to said mammal an amount of a compound of Formula I or Formula II effective in modulating said immune response.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates reaction schemes for the synthesis of partially blocked N-acetyl glucosamine derivatives which are then used to prepare either modified Lewis^c-OR compounds or modified LacNAc compounds.

Figure 2 illustrates reaction schemes for the synthesis of partially blocked galactose derivatives which are then used to prepare either modified Lewis^c-OR compounds or modified LacNAc-OR compounds.

Figure 3A illustrates one method for the preparation of 3-sulfated Lewis^c-OR compounds.

Figure 3B illustrates one method for the preparation of 6-sulfated Lewis^c-OR compounds.

Figure 4 illustrates methods for preparing differentially blocked βGal(1→3)βGlcNAc-OR compounds (Lewis^c-OR) and derivatives thereof and methods for preparing differentially blocked βGal(1→4)βGlcNAc-OR (LacNAc-OR) compounds.

Figure 5 illustrates the synthesis of the 6-azido derivative of GlcNAc-OR.

Figure 6 illustrates the synthesis of the 6-alkoxy derivatives and the 6-deoxy derivatives of GlcNAc-OR.

Figure 7 illustrates the preparation of 3-hydroxy or 4-hydroxy blocked $GlcNH_2$-OR where the amino group is protected as an N-phthalimido group.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

As noted above, the present invention is directed, in part, to the discovery of novel $Lewis^c$-YR and novel LacNAc-YR analogues which, in mammals, including humans, are useful for <u>in vivo</u> modulation (e.g., suppression) of a cell mediated immune response including cell-mediated and immune directed inflammatory responses to an antigen in a sensitized mammal (e.g., a DTH response).

However, prior to discussing this invention in further detail, the following terms will first be defined.

<u>Definitions</u>

As used herein, the following terms have the definitions given below:

The term "cell-mediated immune response in a mammal" refers to those mammalian immune responses which are mediated by cell-cell interactions. Included within this term are cell mediated inflammatory responses to an antigen such as DTH responses as well

as cell-mediated inflammatory responses arising from injury such as frost-bite injury, reperfusion injury, adult respiratory distress syndrome, and the like. Preferably, the cell-mediated immune response is a leucocyte-mediated response.

The term "antigen" refers to any protein, peptide, carbohydrate, nucleic acid or other non-endogenous substance which when exposed to a mammal induces an immune response in that mammal.

Disease conditions believed to be caused by antigen exposure include, by way of example, psoriasis, asthma, dermatitis, rheumatoid arthritis, delayed type hypersensitivity, inflammatory bowel disease, multiple scelorsis, viral pneumonia, bacterial pneumonia, and the like.

The term "sensitized mammal" refers to those mammals which have been previously exposed to an antigen and, accordingly, their immune systems have become educated to that antigen. Typically, initial exposure of an antigen to a mammal primes or educates the mammal's immune response to later exposure to that antigen with minimal inflammation during such initial exposure.

The term "secondary immune response" refers to the effector phase of a mammal's immune response to an antigen to which it has been previously been sensitized. A mammal's secondary immune response is typically accompanied by inflammation at the point of antigen exposure.

The term "period for maximal inflammation" refers to the period of time typically required to achieve maximal inflammation in a sensitized mammal due to exposure to a specific antigen or to the period of time typically required to achieve maximal inflammation in a mammal due to an injury which induces a cell-mediated inflammatory response (e.g., myocardial infarction). This period of time depends on several factors. For example, for inflammation due to injury, the period for maximal inflammation depends on factors such as the type and extent of injury. In a sensitized mammal exposed to an antigen, this period is dependent on factors such as the specific antigen to which the mammal has been exposed, the particular mammalian species exposed to the antigen, etc. Accordingly, the period of time required to effect maximal antigen induced inflammation in a sensitized mammal will vary for, by way of example, asthma as opposed to rheumatoid arthritis.

Moreover, while the specific time required to effect maximal inflammation will vary somewhat in a given mammalian species, the time typically required to effect maximal inflammation for different antigen exposures in human and other mammals resulting in asthma, rheumatoid arthritis, psorasis, DTH, etc. is known in the art or are readily ascertainable by the skilled artisan. For example, in the case of a DTH response in mice, maximal inflammation is typically 24 hours after antigen exposure.

The term "LacNAc" refers to the disaccharide βGal(1→4)βGlcNAc. Because of its relationship to the core structure of type II blood group determinants, the

βGal(1→4)βGlcNAc structure of LacNAc is often referred to as a type II structure.

The term "$LacNH_2$" refers to the LacNAc derivative wherein the N-acetyl group of LacNAc has been replaced with an amine ($-NH_2$).

The term "$LacN_3$" refers to the LacNAc derivative wherein the N-acetyl group of LacNAc has been replaced with an azido ($-N_3$).

The term "$Lewis^c$" (sometimes referred to "Le^c") refers to the disaccharide βGal(1→3)βGlcNAc. Because of its relationship to the core structure of type I blood group determinants, the βGal(1→3)βGlcNAc structure of $Lewis^c$ is often referred as a "type I structure".

The terms "modified $Lewis^c$ glycosides ($Lewis^c$-YR) and derivatives thereof" refer to derivatives of the $Lewis^c$ modified in one or both of the galactose and N-acetylglucosamine saccharide units of $Lewis^c$ and which have an -YR substituent as defined above. When the R substituent is an aglycon group, this group has at least one carbon atom, but nevertheless is different from glycoconjugates because such aglycon moieties are neither a protein nor a lipid capable of forming a micelle or other large aggregate structure.

The term "modified LacNAc glycosides (LacNAc-YR) and derivatives thereof" refer to derivatives of the LacNAc modified in one or both of the galactose and N-acetylglucosamine saccharide units of LacNAc and which have an -YR substituent as defined

above. When the R substituent is an aglycon group, this group has at least one carbon atom, but nevertheless is different from glycoconjugates because such aglycon moieties are neither a protein nor a lipid capable of forming a micelle or other large aggregate structure.

The term "aglycon of at least one carbon atom" refers to non-saccharide containing residues having at least one carbon atom. Preferably, the aglycon moiety, R, is selected from the group consisting of -(A)-Z wherein A represents a bond, an alkylene group of from 2 to 10 carbon atoms, and a moiety of the formula $-(CH_2-CR_{20}G)_n-$ wherein n is an integer equal to 1 to 5; R_{20} is selected from the group consisting of hydrogen, methyl, or ethyl; and G is selected from the group consisting of hydrogen, halogen, oxygen, sulphur, nitrogen, phenyl and phenyl substituted with 1 to 3 substituents selected from the group consisting of amine, hydroxyl, halo, alkyl of from 1 to 4 carbon atoms and alkoxy of from 1 to 4 carbon atoms; and Z is selected from the group consisting of hydrogen, methyl, phenyl, nitrophenyl, aminophenyl and, when G is not oxygen, sulphur or nitrogen and A is not a bond, then Z is also selected from the group consisting of -OH, -SH, $-NH_2$, $-NHR_{21}$, $-N(R_{21})_2$, -C(O)OH, $-C(O)OR_{21}$, $-C(O)NH-NH_2$, $-C(O)NH_2$, $-C(O)NHR_{21}$, $-C(O)N(R_{21})_2$, and $-OR_{22}$ wherein each R_{21} is independently alkyl of from 1 to 4 carbon atoms and R_{22} is an alkenyl group of from 3 to 10 carbon atoms.

Numerous aglycons are known in the art. For example, an aglycon comprising a para-nitrophenyl group (i.e., $-YR = -OC_6H_4pNO_2$) has been disclosed by Ekborg, et al.[18] At the appropriate time during synthesis, the

nitro group is reduced to an amino group which can be protected as N-trifluoroacetamido. The trifluoroacetamido group can later be removed thereby unmasking the amino group which can then be used to further functionalize the aglycon group.

An aglycon containing sulfur is disclosed by Dahmen, et al.[19]. Specifically, the aglycon is derived from a 2-bromoethyl group which, in a substitution reaction with thionucleophiles, has been shown to lead to aglycons possessing a variety of terminal functional groups such as $-OCH_2CH_2SCH_2CO_2CH_3$ and $-OCH_2CH_2SC_6H_4$-pNH_2.

Rana, et al.[20] discloses a 6-trifluoroacetamidohexyl aglycon ($-O-(CH_2)_6-NHCOCF_3$) in which the trifluoroacetamido protecting group can be removed unmasking the primary amino group which can then be used to further functionalize the aglycon group.

Other exemplification of known aglycons include the 7-methoxycarbonyl-3,6,dioxaheptyl aglycon[21] ($-OCH_2-CH_2)_2OCH_2CO_2CH_3$; the 2-(4-methoxycarbonylbutanecarboxamido)ethyl[22] ($-OCH_2CH_2NHC(O)(CH_2)_4CO_2CH_3$); and the allyl aglycon[23] ($OCH_2CH=CH_2$) which, by radical co-polymerization with an appropriate monomer, leads to co-polymers; other allyl aglycons[24] are known [e.g., $-O(CH_2CH_2O)_2CH_2CH=CH_2$]. Additionally, allyl aglycons can be derivatized in the presence of 2-aminoethanethiol[25] to provide for aglycons $-OCH_2CH_2CH_2SCH_2CH_2NH_2$. Still other aglycons are illustrated hereinbelow.

Additionally, as shown by Ratcliffe et al.[9], the R group can be an additional saccharide-OR_{19} or an oligosaccharide-OR_{19} containing an aglycon at the reducing sugar terminus.

Preferably, the aglycon moiety is a hydrophobic group and most preferably, the aglycon moiety is a hydrophobic group selected from the group consisting of $-(CH_2)_8COOCH_3$, $-(CH_2)_5OCH_2CH=CH_2$ and $-(CH_2)_8CH_2OH$.

The term "oligosaccharide" refers to a carbohydrate structure having from 2 to about 7 saccharide units. The particular saccharide units employed are not critical and include, by way of example, all natural and synthetic derivatives of glucose, galactose, N-acetylglucosamine, N-acetyl-galactosamine, fucose, sialic acid, 3-deoxy-D,L-octulosonic acid, and the like. In addition to being in their pyranose form, all saccharide units described herein are in their D form except for fucose which is in its L form.

The term "sialic acid" or "sialyl" means all naturally occurring structures of sialic acid and analogues of sialic acid. Naturally occurring structures of sialic acid include, by way of example, 5-acetamido-3,5-dideoxy-D-glycero-D-galactononulo-pyranosylonic acid ("Neu5Ac"), N-glycoyl neuraminic acid (Neu5Gc) and 9-O-acetyl neuraminic acid ($Neu5,9Ac_2$). Analogues of sialic acid refers to analogues of naturally occurring structures of sialic acid including those wherein the sialic acid unit has been chemically modified so as to introduce and/or remove one or more functionalities from such structures. For example, such modification can result in the removal of an -OH functionality, the introduction of an amine functionality, the introduction of a halo functionality, and the like.

Certain analogues of sialic acid are known in the art and include, by way of example, 9-azido-Neu5Ac, 9-amino-Neu5Ac, 9-deoxy-Neu5Ac, 9-fluoro-Neu5Ac, 9-bromo-Neu5Ac, 7-deoxy-Neu5Ac, 7-epi-Neu5Ac, 7,8-bis-epi-Neu5Ac, 4-O-methyl-Neu5Ac, 4-N-acetyl-Neu5Ac, 4,7-di-deoxy-Neu5Ac, 4-oxo-Neu5Ac, as well as the 6-thio analogues of Neu5Ac. The nomenclature employed herein in describing analogues of sialic acid is as set forth by Reuter et al.[12]

The term "pharmaceutically acceptable salts" includes the pharmaceutically acceptable addition salts of the compounds of Formula I or Formula II derived from a variety of organic and inorganic counter salts well known in the art and include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like.

The term "sulfate" such as used to define the substituents $-X_1$ and $-X_2$ refers to substituents which, with the oxygen of a hydroxyl group of the galactose unit, form a sulfate group (i.e., $-O-S(O)_2-OH$). Thus, when X_1 or X_2 is a sulfate, the resulting $-OX_1$ and/or $-OX_2$ group is $-O-S(O)_2-OH$, which readily forms pharmaceutically acceptable salts thereof (e.g., $-O-S(O)_2-O^-Na^+$). Contrarily, the term "sulfate" as it is used for R_3 refers to the $-O-S(O_2)-OH$ group, which readily forms pharmaceutically acceptable salts thereof.

The term "phosphate" such as used to define the substituents $-X_1$ and $-X_2$ refers to substituents which, with the oxygen of a hydroxyl group of the galactose unit, form a phosphate group (i.e.,

$-O-P(O)-(OH)_2$. Thus, when X_1 or X_2 is a phosphate, the resulting $-OX_1$ and/or $-OX_2$ group is $-O-P(O)-(OH)_2$, which readily forms pharmaceutically acceptable salts thereof (e.g., $-O-P(O)-(O^-Na^+)_2$.

The term "removable blocking group" or "blocking group" refers to any group which when bound to one or more hydroxyl groups of the galactose and/or the N-acetylglucosamine of the Lewis^c-YR and LacNAc-YR compounds prevents reactions from occurring at these hydroxyl groups and which protecting group can be removed by conventional chemical or enzymatic steps to reestablish the hydroxyl group. The particular removable blocking group employed is not critical and preferred removable hydroxyl blocking groups include conventional substituents such as benzyl, benzoyl, acetyl, chloroacetyl, benzylidine, t-butyldiphenyl-silyl and any other group that can be introduced either enzymatically or chemically onto a hydroxyl functionality and later selectively removed either by enzymatic or chemical methods in mild conditions compatible with the nature of the product. One such contemplated blocking group is a α-galactose which can be removed enzymatically with an α-galactosidase.

2. Methodology

The modified Lewis^c-YR and modified LacNAc-YR compounds disclosed herein are readily prepared by complete chemical syntheses.

The figures attached hereto elaborate on a variety of complete chemical synthetic schemes which result in the preparation of modified Lewis^c-YR and modified LacNAc-YR compounds.

Chemical synthesis is a convenient method for preparing either the complete oligosaccharide glycoside; for chemically modifying a saccharide unit which can then be chemically or enzymatically coupled to an oligosaccharide glycoside; or for chemically preparing an oligosaccharide glycoside to which can be enzymatically coupled one or more saccharide units.

Several chemical syntheses of blocked intermediates exist[16,17,30] and, with suitable modifications to these synthetic routes, can be used herein. Syntheses of these intermediates or similar ones utilizing methods known in the art allow the synthesis of the modified Lewis^c-YR and modified LacNAc-YR compounds disclosed herein.

Chemical modifications include introduction of the sulphate or phosphate group or a $-OCHR_{18}COOH$ at the 3 and/or 6 position of the terminal galactose; the introduction of a sulfate at the 2-position of the galactose; and optionally, the introduction of modification at the 2- and 6- positions of the N-acetylglucosamine unit and/or introduction of deoxy or fluoro functionality at the 2-position of the galactose, and the like.

In the description below as well as in the examples and figures, reference is made to the -OR group at the reducing sugar. However, it is understood that this group could also be -NHR or -SR, the preparation of which is well known in the art.

2A. CHEMICAL SYNTHESIS OF SACCHARIDE MONOMERS

Chemical methods for the synthesis of Lewis^c-YR and LacNAc-YR and some analogues thereof are known in the art. These materials are generally assembled using suitably protected individual monosaccharide intermediates. The modifications to the final structures are accomplished using known methods for sulfation or phosphorylation after appropriate selective deblocking of the to-be functionalized hydroxyl group(s) of the fully blocked Lewis^c-YR or LacNAc-YR.

The specific methods employed are generally adapted and optimized for each individual structure to be synthesized. In general, the chemical synthesis of all or part of the these disaccharides first involves formation of a glycosidic linkage on the anomeric carbon atom of the reducing sugar. Specifically, an appropriately protected form of a naturally occurring or of a chemically modified saccharide structure (the glycosyl donor) is selectively modified at the anomeric center of the reducing unit so as to introduce a leaving group comprising halides, trichloroacetimidate, acetyl, thioglycoside, etc. The donor is then reacted under catalytic conditions well known in the art with an aglycon or an appropriate form of a carbohydrate acceptor which possess one free hydroxyl group at the position where the glycosidic linkage is to be established. A large variety of aglycon moieties are known in the art and can be attached with the proper configuration to the anomeric center of the reducing unit. Appropriate use of compatible blocking groups, well known in the art of carbohydrate synthesis, will allow selective modification of the synthesized

structures or the further attachment of additional sugar units or sugar blocks to the acceptor structures.

After formation of the glycosidic linkage, the saccharide glycoside can be used to effect coupling of the galactose unit or chemically modified at selected positions. In general, chemical coupling of a naturally occurring or chemically modified saccharide unit to the saccharide glycoside is accomplished by employing established chemistry well documented in the literature. See, for example, Okamoto et al.[31], Ratcliffe et al.[8], Abbas et al.[32], Paulsen[33], Schmidt[34], Fugedi et al.[35], and Kameyama et al.[36]

With reference to the figures, Figure 1 illustrates the synthesis of numerous blocked derivatives of glucosamine and N-acetylglucosamine which are then useful in the preparation of blocked $LacNH_2$-OR [βGal(1→4)βGlcNH_2-OR], LacNAc-OR [βGal(1→4)βGlcNAc-OR], $Lewis^c$-OR [βGal(1→3)βGlcNAc-OR], $Lewis^c$-NH_2-OR [βGal(1→3)βGlcNH_2-OR], etc. structures. Specifically, in Figure 1, glucosamine hydrochloride is slurried in dichloroethane containing an equivalent of anhydrous sodium acetate to which acetic anhydride is added dropwise and, after addition is completed, the solution is refluxed for a period of from about 12-16 hours to provide for the peracylated compound **10** (about 3:1 ratio of α/β).

Alternatively, the glucosamine hydrochloride is first taken up in methanol and then treated with 1 equivalent of metallic sodium to neutralize the HCl. Phthalic anhydride is then added quickly to the reaction mixture followed shortly thereafter by triethylamine to provide for the phthalimido

derivative. This compound is then isolated and acetylated with acetic anhydride/pyridine using conventional techniques to provide for peracylated compound 1 having a phthalimide blocking group protecting the amine.

Afterwards, the aglycon is formed by conventional techniques. For example, compound 10 is converted to 1-α-chloro compound 2 by well known chemistry which involves bubbling saturating amounts of hydrogen chloride directly into a dichloroethane solution of compound 10. In this regard, the solution used to prepare compound 10 can be used in this reaction after that solution has been quenched into water to remove acetic anhydride and sodium acetate, dried and recovered. The reaction generally proceeds over a period of about 4-6 days and hydrogen chloride is bubbled into the solution periodically (e.g., about once ever 1-2 days). After reaction completion, the solution is quenched in aqueous sodium bicarbonate at about 0-5°C and the product is recovered after drying the organic layer and stripping the solution to provide for compound 2 (one spot on t.l.c.)

Compound 2 is then converted to the 1-β-$(CH_2)_8COOCH_3$ aglycon by well known chemistry which involves reaction of compound 2 with $HO(CH_2)_8COOCH_3$ in anhydrous dichloromethane containing molecular sieves in the presence of an equivalent amount of mercuric cyanide. The reaction is generally conducted at room temperature for a period of about 12 to 24 hours. Upon reaction completion (as evidenced by t.l.c.), the reaction solution is filter through silica and the resulting solution is quenched by adding the reaction solution to cold water. The organic layer is recovered

and the washed twice with an aqueous potassium iodide (5 weight/vol percent) solution and then with a saturated aqueous sodium bicarbonate solution. The resulting organic solution is then dried and the solvent removed by stripping to provide for compound 3.

The 3, 4, and 6 hydroxyl groups of compound 3 are then deprotected by reaction with sodium methoxide in methanol to provide for N-acetylglucosamine-OR, compound 4. This compound can reacted with $C_6H_5CH(OCH_3)_2$ in, for example, an acidic medium in an appropriate solvent at around 40-50°C for about 4-6 hours to provide for the 4,6-O-diprotected benzylidine compound 5. In turn, compound 5 can be reacted with p-methoxybenzyl trichloroacetimidate in an appropriate solvent (e.g., DMF, dichloromethane) in the presence of a catalytic amount of an acid (e.g., p-toluenesulfonic acid -- pTSA) to provide for the p-methoxybenzyl protected 3-hydroxy compound 6. Treatment of compound 6 with sodium cyanoborohydride in tetrahydrofuran followed by the dropwise addition of HCl saturated ether at about 0°C leads to compound 7.

Alternatively, compound 5 can be blocked at the 3-hydroxyl group by reaction with, for example, allyl bromide and base (e.g., barium hydroxide/barium oxide) to provide for compound 8. Treatment of compound 8 with sodium cyanoborohydride in tetrahydrofuran followed by the dropwise addition of HCl saturated ether at about 0°C leads to compound 9.

Because compounds 7 and 9 contain only a free hydroxyl group at the 4-position of the blocked GlcNAc-OR saccharide, subsequent reaction with an

appropriately blocked galactose will result in formation of a blocked type II LacNAc-OR structure [βGal(1→4)βGlcNAc-OR].

Because compound **5** contains a free hydroxyl group only at the 3-position of the blocked GlcNAc-OR saccharide, subsequent reaction with an appropriately blocked galactose will result in formation of a blocked type I structure [βGal(1→3)βGlcNAc-OR].

Alternatively, compound **1** can be converted to compound **11** by reaction of compound **1** with an equivalent of p-chlorothiophenol in dichloromethane at room temperature in the presence of 2 equivalents of boron trifluoride etherate (BF_3·etherate) to provide for compound **11**.

In yet another embodiment, compound **1** is converted to compound **12** (or the bromo analogue) by following similar procedures set forth above for compound **2**.

Compound **12** is converted to compound **13** by reaction with an alcohol (e.g., ethanol, R = $-CH_2CH_3$) in manner similar to that of compound **3** with the exception that the alcohol replaces $HO(CH_2)_8COOCH_3$. Compound **13** is then converted to compound **14** with sodium methoxide/methanol and is then converted to compound **15** by reaction with bis[tributyltin] oxide in refluxing toluene containing tetraethylammonium bromide followed by reaction with benzyl bromide.

Because compound **15** contains free hydroxyl groups at the 3- and 4-positions of the blocked GlcNAc-OR saccharide, subsequent reaction with an appropriate-

ly blocked galactose will result in formation of both a type I structure [βGal(1→3)βGlcNAc-OR] and type II structure [βGal(1→4)βGlcNAc-OR] which are readily separated by conventional techniques including chromatography.

Compound **16** is prepared by treating p-chlorothiophenol with 0.95 equivalents of potassium hydroxide in ethanol followed by heating the solution to about 40-50°C and then adding about 0.5 equivalents of compound **2** to the reaction solution. The reaction is maintained at 40-50°C for about 1-2 hours and the product **16** precipitates upon cooling the solution and is recovered by filtration.

The synthesis of compounds **26** - **31** are depicted in Figure 2 and are set forth in the examples hereinbelow. In this figure, D-galactose pentaacetate **26** is produced by slurring D-galactose and about an equimolar amount (e.g., about 1.1 equivalents) of sodium acetate (NaOAc) in dichloroethane (DCE), heating to reflux and adding at least 5 equivalents of acetic anhydride (AcOAc) dropwise to the refluxing solution (about 80-85°C) and then maintaining the reaction system at this temperature for a sufficient period of time (about 16-32 hours) to result in formation of compound **26**. This procedure optimizes the yield of ß-D-galactose pentaacetate **26** and controls the exotherm of heretofore known procedures.

After workup of the solution, the product is treated with approximately equimolar amounts of benzyl mercaptan ($Ph-CH_2-SH$) and from about 1-3 (preferably two) equivalent of boron trifluoride etherate ($BF_3 \cdot OEt_2$) in dichloromethane. The reaction conditions are not

critical and the reaction is preferably conducted at from about 0°C to about 30°C for a period abouut 6 to 16 hours to yield after crystallization from hot methanol or hot isopropanol 55-65% of benzyl 2,3,4,6-tetra-O-acetyl ß-D-thiogalactopryanoside, compound **27**.

Deacetylation under Zemplen conditions (sodium methoxide/methanol) leads to compound **28**. Deacetylation reaction conditions are not critical and the reaction is generally conducted at room temperature for a period of from about 2 to about 15 hours. After the deacetylation reaction is complete (as judged by t.l.c.), the solution is neutralized with an acid ion exchange resin, filtered and evaporated to dryness to provide for compound **28**. The residue is crystallized from hot acetone and the product is taken up in dimethylformamide or acetonitrile and treated with from 1 to 2 equivalents (preferably 1.4 equivalents) of benzaldehyde dimethyl acetal and about 0.25 to 3 weight percent of p-toluenesulphonic acid (based on compound **28**). The reaction conditions are not critical and preferably the reaction is conducted at room temperature and is generally complete in about 12 to 24 hours. After neutralization, the benzyl 4,6-O-benzylidene ß-D-thiogalactopyranoside, **29**, is isolated and crystallized from hot isopropanol.

Benzyl 4,6-O-benzylidene-3-O-chloroacetyl-ß-D-thiogalactopyranoside **30** is prepared by chloroacetylation using from about 1 to 3 (preferably 2) equivalents of chloroacetylchloride which is added to a dimethylformamide (DMF) solution containing benzyl 4,6-O-benzylidene ß-D-thiogalacto-pyranoside **29**. The chloroacetylchloride is added dropwise while maintaining the DMF solution at from about -40° to

about -15°C (preferably at -25°C). Under these conditions, it is unexpectedly been found that the use of DMF permits selective chloroacetylation of compound 29 without the need for additional base. The reaction is generally complete in about 10-24 hours.

Benzyl 4,6-O-benzylidene-3-O-chloroacetyl-ß-D-thiogalactopyranoside (compound 30) is benzoylated with at least 1 equivalent (and preferably about 2 equivalents) of benzoyl chloride in a suitable solvent containing a base (e.g., pyridine/methylene chloride) with from about 0.1 to about 1 weight percent of dimethylaminopyridine [DMAP] as a catalyst. The reaction conditions are not critical and preferably the reaction is conducted at from about 0°C to about 30°C and for about 1 to about 4 hours (preferably room temperature for 2 hours) to give crystalline benzyl 4,6-O-benzylidene 2-O-benzoyl-3-O-chloroacetyl-ß-D-thio-galactopyranoside, compound 31, in approximately 10-20% overall yield from galactose.

The advantage of this approach is that after subsequent assembly the blocked intermediates will be simply deblocked and modified by sulfation or phosphorylation. The material is crystalline and the process obviates the need for chromatography.

The sulfates and phosphates of the galactose moiety of blocked Lewis^c-YR and LacNAc-YR can also be made using compound 32 in the synthesis of these compounds. This compound is made by direct benzoylation of both the 2,3-hydroxyl groups of compound 29. However, after deblocking, both the 2 and 3 hydroxyl groups of galactose are then available for sulfation and phosphorylation and the selectivity is

not as efficient. Selectivity can be improved by, for example, conducting the sulfation reaction at a low temperature (e.g., -50°C).

Compound **29** can be converted to the 2,3-dibenzoyl protected compound **32** in a manner similar to that described above for the preparation of compound **31**. In this case, 3-5 equivalents of benzoyl chloride are generally employed.

Compounds **31** and **32** are converted to compounds **33** and **32a** (shown in Figure 4) via known methodology (Norberg et al.[26]) using bromine tetraethylammonium bromide.

Alternatively, compound **31** can be converted to compound **34** by contacting compound **31** with 80% acetic acid/water at approximately 50°C for about 1-2 hours. Compound **34** is then converted to compound **35** by treatment with acetic anhydride/pyridine in dichloromethane.

In another embodiment, compound **32** is treated with sodium cyanoborohydride and ceric chloride to provide for the benzyl-2,3-O-dibenzoyl-4-O-benzyl-β-D-thiogalactopyranoside (not shown). In turn, this compound is chloroacetylated at the 6-hydroxyl group. After formation of the Lewis^c-OR or LacNAc-OR blocked structures, the chloroacetyl group can be selectively removed (as described above) and then either phosphorylated or sulphated so as to provide for the 6-phosphate or 6-sulfate derivative.

2B. FORMATION OF TYPE I STRUCTURES HAVING SULFATE SUBSTITUTION AT THE 3 OR 6-POSITIONS OF GALACTOSE

Figure 3A illustrates one method for the preparation of 3-sulfated Lewis^c-OR compounds. Specifically, in Figure 3A, compound **101**, is prepared by reacting N-acetylglucosamine-OR (e.g., compound **4** in Figure 1) with $C_6H_5CH(OCH_3)_2$ in an acidic acetonitrile or dimethylformamide (DMF) medium at from about 0° to about 50°C over 12-48 hours to provide for the 4,6-diprotected benzylidine compound **101**.

About 1 equivalent of N-iodosuccinimide is combined with about 1 equivalent of trifluoromethane-sulfonic acid in methylene chloride containing molecular sieves which remove any water present. The reaction mixture is cooled to -50°C and then compound **101** is added followed by the addition of approximately, 1 to 1.1 equivalents of compound **32** (based on compound **101**). The reaction is allowed to equilibrate to about -20° to 0°C over about 1-3 hours. The reaction solution is then quenched by cooling to -50°C followed by the addition of triethylamine until neutral pH is reached. The solution is filtered through Celite and then washed with a saturated sodium bicarbonate solution and water. The organic layer was dried and stripped in vacuo to provide for fully protected disaccharide **102**.

In this reaction, compound **32a** or **112** can be used in place of compound **32**. Compound **112** is analagous to compound **32a** but has a 4,6-p-methoxy-benzylidine protecting group on the galactose [prepared from compound **28** using $(CH_3O)_2CH-C_6H_4-p-OCH_3$] instead of the benzylidine protecting group of compound **32a**.

The benzoyl groups on disaccharide **102** are removed under Zemplen conditions (NaOMe/MeOH) to provide for disaccharide **103** having free hydroxyl groups at the 2,3 positions of the galactose. Disaccharide **103** is sulfated in DMF at about -30° to -50°C using about 1.1 to 1.5 equivalents of sulfur trioxide/pyridine complex to provide for the 3-sulfated disaccharide **104** as the pyridinium salt. This product contains some 2-sulfated and some 2,3-disulfated material which can be separated by chromatography. The selectivity of the sulfating step is improved by the use of colder temperatures. Alternatively, compound **103** can be chloroacetylated under typical conditions to provide for a mixture of the 2- and 3-chloroacetyl protecting groups. This mixture can be separated by chromatography and the resulting purified components can be used to prepare 2- or 3-sulfated products selectively, or for that matter, the 2-phosphorylated and 2-$OCHR_{18}COOH$ substituents (discussed below), both of which find utility in this invention as immunomodulating compounds.

Passage of a methanol solution of the 3-sulfated disaccharide pyridinium salt, **104**, through Na^+ ion exchange resin provided for the sodium salt, **105**. Compound **105** was deblocked under conventional conditions to provide for the 3-sulfated $Lewis^c$-OR derivative, **106**, not shown.

A differentially protected $Lewis^c$-OR structure can be prepared by combining compound **5** with compound **31** under suitable conditions to provide for a fully blocked $Lewis^c$-OR structure having a 3-chloroacetyl blocking group and a 2-benzoyl blocking group on the galactose unit. This compound can then be

selectively deblocked at the 3-position of the galactose and then sulfated in the manner described above to provide for the 3-sulfated blocked structure. However, deprotection of this product may lead to the generation of by products (e.g., the 2-NH_2 of the GlcNAc). If necessary, these by products can be separated by chromatography.

Figure 3B illustrates one method for preparing the 6-sulfate Lewis^c-OR compound. Specifically, compound **107** is prepared from compound **28** by treating compound **28** with p-anizaldehyde dimethylacetal under conditions otherwise identical to the preparation of compound **29**. The resulting product is benzoylated under conditions similar to those employed to prepare compound **32**. This compound is then ring opened using sodium cyanoborohydride in acidic medium in tetrahydrofuran which yields the free 4-OH derivative which, in turn, is acetylated under typical conditions to provide for compound **107**. Compound **107** is then converted to the 1-α-bromo derivative using Norberg[26] conditions (bromine, tetraethylammonium bromide at 0°C in methylene chloride) to provide for compound **108**.

Compound **108** is then combined with compound **101** in the presence of methylene chloride, silver carbonate (about 3 equivalents), silver triflate (about 0.1 equivalents) and molecular sieves. The reaction is conducted at about 0°C to room temperature for about 5 to about 16 hours to provide for the fully protected Lewis^c-OR derivative, compound **109**. The p-methoxybenzyl blocking group at the 6-position of the galactose unit is selectively removed by contacting compound **109** with dichlorodicyanoquinone (DDQ) in methylene chloride and

a trace of water to provide for compound **110**. Compound **110** is then sulfated at the 6-position of the galactose in DMF at about -50° to 0°C using about 1.1 to 1.5 equivalents of sulfur trioxide/pyridine complex to provide for the 6-sulfated blocked Lewis^c-OR as the pyridinium salt.

Passage of a methanol solution of this sulfated product through a Na^+ ion exchange resin provided for the sodium salt, compound **111**, which upon deblocking provides for compound **121**.

2C. FORMATION OF TYPE II STRUCTURES HAVING SULFATE SUBSTITUTION AT THE 3 OR 6-POSITIONS OF GALACTOSE

Figure 4 illustrates one method for the preparation of intermediates useful in the preparation of 3-sulfated LacNAc-OR compounds. Specifically, in Figure 4, compound 7 and approximately 1.6-1.7 equivalents of compound **32a** are dissolved in dichloromethane containing molecular sieves to which is added about 1 equivalent (based on compound 7) of 2,6-di-t-butyl-4-methylpyridine. The reaction is stirred for 30 minutes at room temperature and then cooled to -50°C. An anhydrous toluene solution containing approximately a slight excess (e.g., about 1.2 equivalents) of silver trifluoromethanesulfonate is then added to the solution and the reaction was allowed to warm to -15°C over 2 hours and maintained at that temperature for an additional 5 hours.

After reaction completion, the reaction system was worked up to provide a crude product of compound **42**. This is then purified by conventional

techniques such as column chromatography using silica gel and toluene-ethyl acetate (1:1) as the eluant.

The benzoyl groups on the protected LacNAc-OR 42 are removed under Zemplen conditions to provide for the LacNAc-OR derivative having free hydroxyl groups at the 2,3 positions of the galactose. This disaccharide is sulfated in DMF at about -30° to -50°C using about 1.1 to 1.5 equivalents of sulfur trioxide/pyridine complex in the manner described above to provide for the blocked 2-hydroxy-3-sulfated LacNAc-OR as the pyridinium salt. This product contains some 2-sulfated and some 2,3-disulfated material which can be separated by chromatography. The selectivity of the sulfating step is improved by the use of colder temperatures.

Alternatively, the 2,3-dihydroxy disaccharide can be chloroacetylated under typical conditions to provide for a mixture of the 2- and 3-chloroacetyl protecting groups. This mixture can be separated by chromatography and the resulting purified components can be used to prepare 2- or 3-sulfated products selectively.

Passage of a methanol solution of the 3-sulfated LacNAc-OR pyridinium salt through Na^+ ion exchange resin provides for the sodium salt and conventional deblocking provides for the 3-sulfated LacNAc-OR derivative.

Figure 4 also illustrates a differentially blocked LacNAc-OR structure which can be used to prepare 3-sulfated structures. Specifically, compound 7 and compound 33 are combined to form compound 37. This is accomplished by dissolving compound 7 and

approximately 1.5 equivalents of compound 33 in dichloromethane containing molecular sieves to which is added about 1 equivalent (based on compound 7) of 2,6-di-t-butyl-4-methylpyridine. The reaction is stirred for 30 minutes at room temperature and then cooled to -50°C. An anhydrous toluene solution containing approximately a slight excess (e.g., about 1.2 equivalents) of silver trifluoromethane sulfonate is then added to the solution and the reaction is allowed to warm to -15°C over 2 hours and maintained at that temperature for an additional 5 hours.

At this time, the molecular sieves are removed by filtration by passing through celite and the recove d solution is quenched by addition to a saturated sodium bicarbonate solution. The organic extract is then washed with water, with aqueous 0.5N HCl, and then with water. The organic solution is then dried and concentrated in vacuo to provide a crude product, compound 37. This is then purified by conventional techniques such as column chromatography using silica gel and hexane-ethyl acetate (1:1) as the eluant.

Compound 37 is then selectively deblocked at the 3-position of the galactose and then sulfated in the manner described above to provide for the 3-sulfated blocked structure. However, deprotection of this product may lead to the generation of by products (e.g., the 2-NH_2 of the GlcNAc). If necessary, these by products can be separated by chromatography.

The 6-sulfate derivative of LacNAc-OR is prepared in the manner described above for the

6-sulfate of Lewis^c-OR with the exception that compounds **7** or **9** are used in place of compound **101** in this reaction.

2D. FORMATION OF TYPE I AND II STRUCTURES HAVING PHOSPHATE OR -$CHR_{18}COOH$ SUBSTITUTION AT THE 3- OR 6-POSITIONS OF GALACTOSE

Blocked Lewis^c-OR and blocked LacNAc-OR compounds having a 2, 3- or 6-hydroxyl group (e.g., compound **103**) on the galactose unit can be can be converted to the 2-, 3-, 6-phosphate group on the galactose by reaction with diphenylphosphorochloridate and 4-dimethylaminopyridine (1:1) in pyridine at 0°C[16]. The solution is allowed to warm to room temperature over 0.5 hours and stirred for 15 hours. The resulting compound is then hydrogenated under conventional conditions (first with H_2 in EtOH with Pd on carbon for 15 hours and then with H_2 in EtOH with PtO_2 for 3 hours) to provide for the phosphate derivative at the 2-, 3-or 6-position of galactose. Deprotection leads to the modified Lewis^c-OR and LacNAc-OR compounds having a phosphate substituent at the 2-, 3-, 6-position of galactose which is purified and converted to its disodium salt by contacting a solution of this compound with a sodium form of Dowex 50 x 8.

In another embodiment, blocked Lewis^c-OR and blocked LacNAc-OR compounds having a 2-, 3- or 6-hydroxyl group (e.g., compound **103**) on the galactose unit can then be alkylated by first adding an appropriated base (e.g., silver oxide, barium hydroxide, sodium hydride) and then adding benzyl bromoacetate ($BrCH_2COOBn$) or other similar acetates (e.g., $BrCHR_{18'}COOBn$ -- where $R_{18'}$ is alkyl of from 1 to 7 carbon atoms or -COOBn) to the reaction medium in an

appropriate solvent such as DMF. After reaction completion, the benzyl ester(s) is (are) readily removed by conventional hydrogenation techniques which additionally removes the other benzyl protecting groups and the benzylidine protecting group. Treatment with sodium methoxide/methanol provides for a $-OCH_2COOH$ (or $-OCHR_{18}COOH$ where R_{18} is alkyl of from 1 to 7 carbon atoms or -COOH) substituted to the 2-, 3-, 6-position of galactose.

2E. MODIFICATION ON THE 2 AND/OR 6 POSITIONS OF GlcNAc

The 2,6 positions of the GlcNAc unit can be modified prior to coupling so as to provide for $Lewis^c$-OR and LacNAc-OR structures modified at these positions which are then further modified in the manner described above to prepare the sulfated, phosphorylated or $-CHR_{18}COOH$ derivatives. In any event, functionalization of the GlcNAc unit at the 2,6 position is generally at a point in the synthesis where the to-be formed functional group does not interfere with any of the further intended reactions. For example, if an R_1 functional group in GlcNAc-OR would interfere with the coupling reaction with the blocked galactose, then the functional group can either be introduced at the disaccharide level or blocked at the monosaccharide level (e.g., 2-amino groups are conventionally blocked with as the N-trifluoroacetamido or the N-phthalimido group) and later deblocked.

i. Modification at the 2-position of GlcNAc

Modification at the 2-position of GlcNAc can be accomplished by a variety of ways. For example, the

known[8,9] 2-azido-2-deoxy-glucose-OR compound (prepared, for example, by azidonitration of 4,5,6-triacetylglucal) can be protected at the 6 position with a removable protecting group (i.e., $Si(C_6H_5)_2tBu$) by conventional techniques[8,9] and then combined with an appropriate blocked galactose compound in the manner described above to provide for the blocked $\beta Gal(1\rightarrow3)GlcN_3$-OR and $\beta Gal(1\rightarrow4)GlcN_3$-OR derivatives which are readily separated by conventional techniques.

At the appropriate time during synthesis of the Lewis^c-OR and LacNAc-OR structures, the azido group is reduced to an amino group which can be protected, for example, as N-trifluoroacetamido. In turn, the trifluoroacetamido group is removed at the appropriate point in the synthesis thereby unmasking the amino group.

The amino group can also be derivatized by conventional methods to provide for $-NR_{11}C(O)R_{10}$, $-NHSO_3H$, $-N=C(R_{11})_2$, $-NHCH((R_{11})_2$, $-NHR_{12}$, and $-N(R_{12})_2$ groups. For example, the $-NH_2$ group can be reacted, using conventional techniques:

with a carboxylic acid, anhydride or chloride to provide for amides. Alternatively, the desired acid can be activated, as reported by Inazu et al[37] and then reacted with the amino group. The carboxylic acid, anhydride, chloride, or activated acid is selected so as to provide for an R_{10} group (i.e., as part of the $-NR_{11}C(O)R_{10}$ substituent) which is hydrogen or alkyl of from 1 to 4 carbon atoms,

with an aldehyde or ketone (of from 1 to 4 carbon atoms) at controlled pH to form an imine [$-N=C(R_{11})_2$] which upon reduction (e.g., with sodium cyanoboro-

hydride) provides for an alkylamine substituent [i.e., $-NHCH(R_{11})_2$] as reported by Bernotas et al.[38],

with a cyclic carbonate such as ethylene carbonate or propylene carbonate which ring opens upon reaction with the amine to form a carbamate group having an HO-alkylene-OC(O)NH- substituent where alkylene is from 2 to 4 carbon atoms as reported by Wollenberg et al.[39], U.S. Patent No. 4,612,132,

with a chloroformate [i.e., $ClC(O)OR_{13}$] in the manner disclosed by Greig et al.[40]. In this case, the chloroformate has an R_{13} group which is alkyl of from 1 to 4 carbon atoms,

with $O=C(O-C_6H_4-pNO_2)_2$ which leads to an activated intermediate which is then reacted with an amine ($HNR_{14}R_{15}$) to provide for ureas [$-NHC(O)NR_{14}R_{15}$] as described by Piekarska-Bartoszewicz et al.[41],

with trimethylamine, sulfur trioxide (SO_3) so as to form the $-NHSO_3H$ group as described by Petitou[27], and

with derivatized formic acid or other materials to form a formamide (-NH-CHO)[28] which can be further functionalized to the isocyano (-N=C=O) and reduced to the deoxy derivative by tributyltin hydride (Bu_3SnH)[28].

Alternatively, the 2-deoxy (R_2 = H) and 2-alkoxy glucose derivatives [i.e., derivatives of GlcNAc where the NAc has been replaced by -H (deoxy) or by an $-OR_{12}$ (alkoxy)] are prepared using a synthetic scheme similar to that recited by Trumtez et al.[28] Specifically, the known 3,4,6-triacylated 1,2-ortho ester of glucose is deacylated under conventional conditions to give the 1,2-ortho ester of glucose. This compound is then converted to the 3,4,6-tribenzyl 1,2-ortho ester of glucose using conventional techniques. The 1,2-ortho ester of the resulting

compound is then opened by conventional techniques to provide a protected glycosyl donor such as the 1-α-bromo-2-acetyl-3,4,6-tribenzyl derivative of glucose. This 1-α-bromo derivative is then converted to the glycoside (-OR) by conventional techniques and the 2-acetyl group is then removed. The 2-position is now ready for formation of the 2-deoxy by conventional methods such as first treating with carbon disulfide and methyl iodide in the presence of one equivalent of a base to form the $-C(S)SCH_3$ derivative, followed by reaction with tributyltin hydride) or for the preparation of the 2-alkoxy. The remaining protecting groups are removed so as to provide for 2-deoxyglucose glycoside or a 2-alkoxyglucose glycoside which can then be derivatized in the manner described above and illustrated in Figure 1 without the need to form the aglycon.

ii. Modification at the 6-Position of GlcNAc

As shown in Figure 6, the 6-deoxy derivative of GlcNAc-OR is synthesized from a known benzylidene ring blocked saccharide (8-methoxycarbonyloctyl-2-acetamido-4,6-O-benzylidene-2-deoxy-β-D-gluco-pyranoside)[29] which is protected at the 3-hydroxy position with a removable benzoyl blocking group (Bz) by reaction with benzoic anhydride in pyridine. Further conversion of this compound by reaction with N-bromosuccinimide and barium carbonate in carbon tetrachloride (CCl_4) at 65°C leads to the 3,4-dibenzoyl-6-bromo-GlcNAc-OR compound. This compound is, in turn, converted to the 3,4-dibenzyl-6-deoxy-GlcNAc-OR by reaction with $(C_4H_9)_3SnH$ in the presence of AIBN (azo bis-isobutyronitrile) at 110°C followed by treatment with methanol/sodium methoxide. This compound can then be deprotected by conventional

techniques to provide for the 6-deoxyGlcNAc-OR glycoside which can then be derivatized in the manner described above and illustrated in Figure 1 without the need to form the aglycon.

The 6-azido derivatives of GlcNAc-OR can be prepared in the manner described in Figure 5. Specifically, GlcNAc-OR, compound **87**, is converted to the p-methoxybenzylidine blocked compound **88** by reaction with $(CH_3O)_2CH-C_6H_4-p-OCH_3$. This compound is then protected at the 3-hydroxyl position by reaction with $4-CH_3O-C_6H_4-CH_2Br$ to provide for compound **89** where X is $4-CH_3O-C_6H_4-CH_2-$. Compound **89** is partially deprotected at the 4 and 6 positions by reaction with acetic acid (AcOH) in water at about 45°C to provide for compound **90**. The 6-mesylate, compound **91**, is prepared by reacting compound **90** with mesyl chloride in pyridine (MsCl/py). The 6-azido derivative, compound **92**, is then formed by reaction with sodium azide in dimethylformamide (DMF) and removal of the 3-blocking group with dichlorodicyanoquinone (DDQ) yields compound **93**.

The 6-mesyl compound **91** can also be derivatized to any of a number of 6-substituents including alkoxy substituents, and the like by well known chemistry.

The 6-azido compound **92** can be derivatized to the 6-amino at an appropriate point in the synthesis of the Lewis^c-OR or LacNAc-OR analogues in the manner described above. The 6-amino derivative can then be further functionalized by conventional methods to provide for $-NR_5C(O)R_4$, $-NHSO_3H$, $-N=C(R_5)_2$, $-NHCH(R_5)_2$,

$-NHR_6$ and $-N(R_6)_2$. For example, the $-NH_2$ group can be reacted, using conventional techniques, with:

a carboxylic acid, anhydride or chloride to provide for amides. Alternatively, the desired acid can be activated, as reported by Inazu et al[37] and then reacted with the amino group. The carboxylic acid, anhydride, chloride, or activated acid is selected so as to provide for an R_4 group (i.e., as part of the $-NR_5C(O)R_4$ substituent) which is hydrogen or alkyl of from 1 to 4 carbon atoms,

with an aldehyde or ketone (of from 1 to 4 carbon atoms) at controlled pH to form an imine [$-N=C(R_5)_2$] which upon reduction (e.g., with sodium cyanoborohydride) provides for an alkylamine substituent [i.e., $-NHCH(R_5)_2$] as reported by Bernotas et al.[38],

with a cyclic carbonate such as ethylene carbonate or propylene carbonate which ring opens upon reaction with the amine to form a carbamate group having an HO-alkylene-OC(O)NH- substituent where alkylene is from 2 to 4 carbon atoms as reported by Wollenberg et al.[39], U.S. Patent No. 4,612,132,

with a chloroformate [i.e., $ClC(O)OR_7$] in the manner disclosed by Greig et al.[40]. In this case, the chloroformate has an R_7 group which is alkyl of from 1 to 4 carbon atoms,

with $O=C(O-C_6H_4-pNO_2)_2$ which leads to an activated intermediate which is then reacted with an amine (HNR_8R_9) to provide for ureas [$-NHC(O)NR_8R_9$] as described by Piekarska-Bartoszewicz et al.[41],

with trimethylamine, sulfur trioxide (SO_3) at pH 9.5 so as to form the $-NHSO_3H$ group as described by Petitou[27], and

with derivatized formic acid or other materials to form a formamide ($-NH-CHO$)[28] which can be further

functionalized to the isocyano (-N=C=O) and reduced to the deoxy derivative by tributyltin hydride (Bu_3SnH)[28].

The 6-alkoxy derivatives of GlcNAc can be prepared in the manner described in Figure 6. Specifically, GlcNAc-OR, compound **87**, is reacted with $C_6H_5CH(OCH_3)_2$ in an acidic medium in acetonitrile to provide for the 4,6-diprotected benzylidine compound **94**. In turn, compound **94** can be reacted with benzyl (Bn) bromide and sodium hydride in the presence of dimethylformamide at around 0°C to provide for a benzyl protecting group at the 3-position, i.e., compound **95**. Deprotection at the 4,6 positions by contacting compound **95** with acetic acid and water at about 80°-90°C provides for compound **96**. Reaction of compound **96** with dibutyltin oxide [$(Bu)_2SnO$] and R_6Br provides for the 6-alkoxy compound **97**. Conventional deprotection of the benzyl group with hydrogen in palladium/carbon yields compound **98**.

In another embodiment, compound **94** can be reacted with $[C_6H_5C(O)]_2O$ in pyridine to provide for a benzoyl protecting group (Bz) at the 3-position, i.e., compound **99**. Reaction of compound **99** with N-bromo-succinimide in carbon tetrachloride yields the 6-bromo compound **100**. Compound **100** can be reacted with tributyltin hydride [$(Bu)_3SnH$] in toluene to provide for the 6-deoxy compound **100b** which after conventional deprotection of the benzoyl groups with sodium methoxide in methanol gives the 6-deoxy compound **100c**.

The 6-SR_6 compounds are prepared from the 6-mesyl derivative, compound **91**, by reaction with potassium thioacetate, $CH_3C(O)S^-K^+$, to give the thioacetate derivative at the 6-position. This

derivative is then treated with mild base to produce the 6-SH derivative. The 6-SH can be reacted with an alkyl halide (e.g., CH_3Br) to provide the $-SR_6$ derivatives which, in turn, can be partially or fully oxidized to the 6-sulfone or the 6-sulfoxide derivatives, $-S(O)R_6$ and $-S(O)_2R_6$ where R_6 is alkyl of from 1 to 4 carbon atoms.

Figure 7 illustrates the preparation of 3-hydroxy or 4-hydroxy blocked $GlcNH_2$-OR where the amino group is protected as an N-phthalimido group. Specifically, in Figure 7, compound **13** is prepared by the methods described above. This compound is then deacetylated by conventional techniques (sodium methoxide/methanol) to provide for compound **14** which is then benzylidenated under conventional techniques to provide compound **66**. Compound **66** is then treated with benzyl chloride and sodium hydride in dimethylformamide at about -20°C to 20°C to provide for compound **67**. The benzylidine group of compound **67** is then removed with 80% aqueous acetic acid at about 80°C for about 1-4 hours to provide for compound **68**. This compound is then selectively acetylated at the 6-position by use of approximately equimolar amounts of acetyl chloride/pyridine in dichloromethane at about -10°C to provide for compound **69**.

As is apparent, compound **69** is useful in preparing $LacNH_2$ derivatives whereas compound **66** is useful in preparing $Lewis^x$-OR derivatives.

The 2- or 3-sulfate, phosphate or $-OCHR_{18}COOH$ substituted LacNAc structures can be converted to the 6-sialyl derivatives by use of the known $\beta Gal(1\rightarrow4)\beta GlcNAc\ \alpha(2\rightarrow6)$sialyltransferase in a manner

similar to that described in the examples herein below. The 6-sialyl derivatives of Lewis^c-OR can be prepared in a manner similar to that of Ratcliffe et al.[12,23] making the appropriate modifications to the blocking groups to allow for subsequent substitution with a sulfate, phosphate or $-CHR_{18}COOH$ group at the 2- or 3-positions of galactose.

C. Utility

Without being limited to any theory, it is believed that the modified Lewis^c-YR and LacNAc-YR compounds disclosed herein affect the cell mediated immune response in a number of ways. Specifically, these compounds can inhibit the ability of the immune response to become educated about a specific antigen when the compound is administered simultaneously with the first exposure of the immune system to the antigen.

Also, the modified Lewis^c-YR and LacNAc-YR compounds disclosed herein can inhibit the secondary immune response to an antigen in a sensitized mammal when administered after second or later exposures of the immune system to the same antigen. Additionally, the modified Lewis^c-YR and LacNAc-YR compounds disclosed herein can induce tolerance to antigens when administered at the time of second or later exposures of the immune system to the antigen.

The suppression of the inflammatory component of the secondary immune response by the modified Lewis^c-YR and LacNAc-YR compounds disclosed herein requires administering such compounds after initiation of the mammal's secondary immune response but at or prior to one-half the period required for maximal antigen induced inflammation. This criticality is

disclosed in U.S. Patent Application No. 07/988,518 filed concurrently herewith as Attorney Docket No. 000475-045 and entitled "TIME DEPENDENT ADMINISTRATION OF OLIGOSACCHARIDE GLYCOSIDES RELATED TO BLOOD GROUP DETERMINANTS HAVING A TYPE I OR TYPE II CORE STRUCTURE IN REDUCING INFLAMMATION IN A SENSITIZED MAMMAL ARISING FROM EXPOSURE TO AN ANTIGEN" which application is incorporated herein by reference in its entirety.

In this embodiment, the modified Lewis^c-OR and LacNAc-OR compounds are preferably administered to the patient at least about 0.5 hours after antigen exposure, more preferably, at least about 1 to 10 hour after antigen exposure, and still more preferably, from about at least about 1 to 5 hours after antigen exposure.

Similarly, in cell-mediated inflammatory responses arising from injuries (e.g., adult respiratory distress injury (lung injury), administration of the Lewis^c-YR and LacNAc-YR is also conducted after initiation of the immune response to this injury but at or prior to one-half the period required for maximal inflammation.

The modified Lewis^c-YR and LacNAc-OR glycosides disclosed herein are effective in suppressing cell-mediated immune responses including cell-mediated immune response to an antigen (eg. the inflammatory component of a DTH response) as well as in suppressing cell-mediated inflammatory responses to injury (e.g., lung injury) when administered at a dosage range of from about 0.5 mg to about 50 mg/kg of body weight, and preferably from about 0.5 to about 5 mg/kg of body weight. The specific dose employed is

regulated by the particular cell-mediated immune response being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the adverse immune response, the age and general condition of the patient, and the like. The modified Lewis^c-YR or LacNAc-YR analogues are generally administered parenterally, such as intranasally, intrapulmonarily, transdermally and intravenously, although other forms of administration are contemplated.

In addition to providing suppression of a mammal's secondary immune response to an antigen, administration of the modified Lewis^c-YR and LacNAc-YR compounds disclosed herein also imparts a tolerance to additional challenges from the same antigen provided that the compound is administered during the critical period discussed above. In this regard, re-challenge by the same antigen weeks after administration of the modified Lewis^c-YR or LacNAc-YR compounds results in a significantly reduced immune response.

Administration of the modified Lewis^c-YR and LacNAc-YR compounds disclosed herein simultaneously with first exposure to an antigen (i.e., a non-sensitized mammal) imparts suppression of a cell-mediated immune response to the antigen and tolerance to future challenges with that antigen. In this regard the term "reducing sensitization" means that the modified Lewis^c-YR or LacNAc-YR compound, when administered to a mammal in an effective amount along with a sufficient amount of antigen to induce an immune response, reduces the ability of the immune system of the mammal to become educated and thus sensitized to the antigen administered at the same time as the

modified Lewis^c-YR or LacNAc-YR compound. An "effective amount" of this compound is that amount which will reduce sensitization (immunological education) of a mammal, including humans, to an antigen administered simultaneously as determined by a reduction in a cell-mediated response to the antigen such as DTH responses as tested by the footpad challenge test. Preferably the reduction in sensitization will be at least about 20% and more preferably at least about 30% or more. Generally, modified Lewis^c-YR and LacNAc-YR compounds disclosed herein are effective in reducing sensitization when administered at a dosage range of from about 0.5 mg to about 50 mg/kg of body weight, and preferably from about 0.5 mg to about 5 mg/kg of body weight. The specific dose employed is regulated by the sensitization being treated as well as the judgement of the attending clinician depending upon the age and general condition of the patient and the like. "Simultaneous" administration of the compound with the antigen with regard to inhibiting sensitization means that the compound is administered once or continuously throughout a period of time within 3 hours of the administration of an antigen, more preferably the compound is administered within 1 hour of the antigen.

The methods of this invention are generally achieved by use of a pharmaceutical composition suitable for use in the parenteral administration of an effective amount of a Lewis^c-YR or a LacNAc-YR compound. These compositions comprise a pharmaceutically inert carrier such as water, buffered saline, etc. and an effective amount of a modified Lewis^c-YR or LacNAc-YR compound so as to provide the above-noted dosage of these compounds when administered

to a patient. It is contemplated that suitable pharmaceutical compositions can additionally contain optional components such as a preservative, etc.

It is also contemplated that other suitable pharmaceutical compositions can include oral compositions, transdermal compositions or bandages etc., which are well known in the art.

It is also contemplated that mixtures of these compounds can be used.

The following examples are offered to illustrate this invention and are not to be construed in any way as limiting the scope of this invention. Unless otherwise stated, all temperatures are in degrees Celsius. Also, in these examples, unless otherwise defined below, the abbreviations employed have their generally accepted meaning:

Å	=	Angstroms
AB	=	AB pattern
ax	=	axial
bs	=	broad singlet
BSA	=	bovine serum albumin
^{13}C-n.m.r	=	C^{13} nuclear magnetic resonance
d	=	doublet
dd	=	doublet of doublets
ddd	=	doublet of doublets of doublets
DDQ	=	dichlorodicyanoquinone
DTH	=	delayed-type hypersensitivity
eq	=	equatorial
g	=	gram
^{1}H-n.m.r.	=	proton nuclear magnetic resonance
i.r.	=	infra red
kg	=	kilogram
L	=	liter
m	=	multiplet
mL	=	milliliter
q	=	quartet
s	=	singlet
t	=	triplet
t.l.c.	=	thin layer chromatography
U	=	Units
μm	=	microns

AG 1 X 8 (formate form) = ion exchange resin AG 1 x 8 (formate form) available from Bio-Rad Laboratories, Richmond, CA

Dowex 50W X 8 (H^+ form) = ion exchange resin Dowex 50 X 8 (H^+ form) available from Dow Chemical, Midland, MI

IR-120 resin (H^+ form) = amberlite resin available from Rohm & Haas, Philadelphia, PA

IR-C50 resin (H^+ form) = ion exchange resin IR-C50 (H^+ form) available from Rohm & Haas, Philadelphia, PA

Commercially available components are listed by manufacturer and where appropriate, the order number. Some of the recited manufacturers are as follows:

Merck = E. Merck AG, Darmstadt, Germany

Millipore = Millipore Corp., Bedford, MA.

Waters = Waters Associates, Inc., Milford, MA.

The following examples are divided into two parts. The first part (part I) relates to the synthetic procedures to make the recited compounds whereas the second part (part II) relates to the biological results.

Part I -- Synthetic Procedures

Examples 1-18 illustrate syntheses of the described compounds.

EXAMPLE 1 -- Synthesis of Benzyl-2-O-benzoyl-4,6-O-benzylidene-3-O-chloroacetyl-ß-D-thiogalactopyranoside (compound 31)

Dry a 20 L stirred reactor equipped with reflux condenser, heating mantle and 1 L addition funnel. Charge to this reactor 10 L of dichloroethane. Begin to stir the reactor then charge 1 kg D-galactose and 500 g anhydrous sodium acetate to the dichloroethane. Heat this slurry to reflux. Add dropwise 4 L of acetic anhydride to the reaction mixture using the 1 L addition funnel on the reactor. Reflux is to be maintained during the 2-4 hour addition period. Continue to stir and heat the mixture at reflux overnight.

When the reaction is complete as determined by t.l.c., turn off the heat to the reactor and add 250 mL of water in slow dropwise fashion using the addition funnel. This reaction is quite vigorous but is controlled by slowing the addition of the water. Stir the reaction for 1-2 hours. Charge 30 L of cold water to a 50 L stirred reactor and begin stirring. Drain the contents of the 20 L reactor into a 20 L polyethylene pail and pour into the stirring ice water in the 50 L reactor. Stir this mixture for twenty minutes. Drain the lower organic layer into a 20 L polyethylene pail. Extract the aqueous layer in the 50 L reactor with an additional 5 L of dichloromethane. Combine the dichloromethane extract with the first organic layer. Drain the aqueous layer to polyethylene pails and discard as aqueous waste.

Return the combined organic layers to the 50 L reactor and extract twice with 5 L portions of ice water for 10 minutes. Drain the organic layer to a clean 20 L polyethylene pail. Drain the aqueous to waste, return the organic layer to the 50 L reactor, stir and add 1 kg of anhydrous sodium sulfate. Stir for 1-2

hours and then drain the solution into a clean 20 L polyethylene pail and filter the solution using a 4 L vacuum filtration set [or large Buchner attached to a collector].

Concentrate the filtrate to 8 L then transfer into a clean 20 L reactor equipped with stirrer, 1 L addition funnel and cooling bath. Additional solvent can be added if the level of the solution is below the thermowell. Cool the organic solution to 0°C using a cooling bath. Charge to this cool solution 724 g of benzyl mercaptan. Add a total of 1.1 L of colorless boron trifluoride etherate in slow dropwise fashion over 2 hours using the 1 L addition funnel. Stir the reaction 3-4 hours after the addition is complete maintaining the temperature at 0°C. The reaction is checked for completion by t.l.c. on silica gel. [The reaction can be left to sit overnight].

The reaction mixture is drained into a clean 20 L polyethylene pail. The 50 L reactor is charged with 15 L of saturated sodium carbonate solution. The 20 L polyethylene pail is slowly transferred into the slowly stirring carbonate solution at such a rate that the gas evolution is not overly vigorous. Stir the solution for 20 minutes then increase the rate of stirring. When gas evolution ceases bubble air through the entire solution for 24-36 hours. Drain the organic layer into a clean 20 L polyethylene pail and store in a hood. Extract the sodium carbonate solution with 3-5 L of dichloromethane and drain this solution into the same 20 L polyethylene pail.

Once the smell has been reduced the organic solution can be filtered using a 4 L vacuum filtration set and the filtrate evaporated under reduced pressure on the 20 L rotovap. 7 L of methanol is introduced into the rotavap flask and the residue heated with the

rotavap bath till the residue dissolves in the warm methanol. The flask is rotated and allowed to cool. Cool ice water is added to the rotavap bath and the flask slowly rotated for several hours. The flask is removed from the rotovap and the white crystalline product filtered using a 4 L vacuum filtration set.

The benzyl 2,3,4,6-tetra-O-acetyl-ß-D-thiogalactopyranoside (~1.3 kg) is charged into a clean dry 20 L reactor with stirring motor and 7 L of dry methanol is added to dissolve the material. The solution is treated with 3 g of freshly surfaced sodium and stirred for two hours. The reaction is checked by t.l.c. on silica gel using a retained sample of the benzyl 2,3,4,6-tetra-O-acetyl-ß-D-thiogalactopyranoside with 80:20 ethyl acetate: methanol (v/v) the eluant. The absence of starting material indicates the reaction is complete.

50 g of fresh methanol washed H^+ ion exchange resin is added, the reaction stirred for 15 minutes. The pH is checked using pH paper to ensure a neutral solution. The resin is filtered off under reduced pressure and the methanol is removed under reduced pressure using the 20L rotovap. To the residue, 5 L of acetone is added to the 20 L flask and the solution warmed to reflux. The residue dissolves and is allowed to cool to room temperature at which time ice is added to the bath, the solution rotated with cooling overnight. 800-900g of benzyl ß-D-thiogalactopyranoside crystallizes and is filtered and dried under vacuum.

To 8 L of dry acetonitrile is added 800 g of benzyl ß-D-galactopyranose, 600 g of benzaldehyde dimethyl acetal and 2-5 g of p-toluenesulphonic acid. The solution is stirred at room temperature overnight. The reaction progress is checked b t.l.c. When

complete, the reaction is brought to pH 7 by the addition of triethylamine. The volume of acetonitrile is reduced to a minimum, 7 L of isopropanol is added and the mixture is heated to near reflux. Most of the product goes into the hot isopropanol after warming for several hours. The mixture is cooled and ice added to the bath and cooling continued overnight to give a precipitate. After filtering and drying the precipitate, 760 g of benzyl-4,6-O-benzylidene-ß-D-thiogalactopyranoside is obtained.

180 g of benzyl-4,6-O-benzylidene-ß-D-thiogalactopyranoside was dissolved in dry DMF and placed in a jacketed reactor. The reactor was cooled using a recirculating cooling bath maintained at a temperature of -25°C and treated dropwise with 108 g of chloroacetyl chloride over 3 hours while stirring the reaction mixture. Stirring was continued 24 hours at this temperature then the reaction was quenched into several volumes of cold bicarbonate solution. The product was extracted into methylene chloride, water washed several times, dried over sodium sulphate and evaporated to dryness. The product was crystallized from isopropanol. Yield: 125 g of benzyl 4,6-O-benzylidene-3-O-chloroacetyl-ß-D-thiogalacto-pyranoside.

5 g Benzyl 4,6-O-benzylidene-3-O-chloroacetyl-ß-D-thiogalactopyranoside was benzoylated at room temperature in methylene chloride/pyridine using 3 equivalents of benzoyl chloride and a catalytic amount of dimethylaminopyridine. The solution is quenched into cold sodium bicarbonate solution, the organic layer is washed with saturated copper sulphate solution to remove the pyridine the organic layer dried and evaporated. The residue is taken up in hot isopropanol and benzyl 4,6-O-benzylidene-2-O-benzoyl-3-O-

chloroacetyl-ß-D-thiogalactopyranoside crystallizes from solution. ^{1}H-n.m.r. ($CDCl_3$): δ = 7.96, 7.4 (2m, 15H, aromatic, 5.79 (t, 1H, H-2), 5.5 (s, 1H, CH), 5.2 (q, 1H, H-4, $J_{2,3}$ 9.9 Hz, $J_{3,4}$ 3.3 Hz), 4.5 (m, 2H), 4.4 (d, 1H), 3.99 (m, 5H), 3.55 (s, 1H).

Example 2 -- Synthesis of 4,6-O-benzylidene-2,3-di-O-benzoyl-ß-D-galactopyranosyl bromide (compound **32A**)

Benzyl-4,6-O-benzylidene-β-D-thiogalactopyranoside (10 g) was dissolved in 100 mL dichloromethane and 6.35 g of pyridine was added. To the solution was added 9 g of benzoyl chloride in dropwise fashion and after 1 hour, 50 mg of dimethylaminopyridine was added to the solution and the mixture was stirred for an addition 2 to 4 hours. The progress of the reaction was checked by t.l.c. on silica gel. Benzyl-4,6-O-benzylidene-2,3-di-O-benzoyl-β-D-thiogalactopyranoside (compound **32**) was isolated by quenching the reaction mixture into saturated sodium bicarbonate solution and washing the organic extract with water, 5% copper sulfate solution, water, drying and evaporating the solvent. The residue was crystallized from isopropanol to give 10.7 g of compound **32**.

Compound **32**, benzyl-4,6-O-benzylidene-2,3-di-O-benzoyl-β-D-thiogalactopyranoside (9.89 g), was dissolved in 100 mL of dichloromethane, cooled to 0°C, and treated with a solution of bromine (2.85 g) in 10 mL of dichloromethane. After 15 minutes, 1.8 grams of tetraethylammonium bromide was added to the mixture and the mixture stirred for 2-3 hours at room temperature (followed by t.l.c. on silica gel). A small quantity of cyclohexane was added to quench excess bromine and the reaction mixture was quenched into cold saturate

sodium bicarbonate solution, washed with water, dried and volume of the solution reduced to 30 mL. This dichloromethane solution of compound **32a** was used directly in the synthesis of compound **42** without further isolation and/or purification.

Example 3 -- Synthesis of 8-methoxycarbonyloctyl-2-acetamido-4,6-di-O-benzylidene-2-deoxy-ß-D-glucopyranoside (Compound 5)

A 20L glass reactor was charged with 8 L of dichloroethane, 1 L of acetic anhydride and 1 kg of anhydrous sodium acetate. To the stirring mixture was added 1 kg of glucosamine hydrochloride and the mixture was brought to reflux. A further 3.5 L of acetic anhydride was added dropwise to the refluxing solution over 3-4 hours and the solution maintained at reflux for 36 hours. During the last hour of reflux 200 mL of water was added dropwise to the solution. The reaction was then cooled and added to 35 L of ice water in a 50 L stirred reactor. The organic layer was removed and then water washed a second time with an additional 20 L of water. The organic layer was dried over sodium sulphate, filtered, and saturated with anhydrous gaseous HCl for 2 hours. The reaction was allowed to sit for 6 days being saturated with HCl for 1 hour every second day. 2-acetamido-2-deoxy-3,4,6-tri-O-acetyl-ß-D-glucopyranosyl chloride was isolated by quenching into ice cold sodium bicarbonate solution. The organic layer was dried over sodium sulphate and evaporated to a brown solid.

Four hundred grams of 2-acetamido-2-deoxy-3,4,6-tri-O-acetyl-ß-D-glucopyranosyl chloride was dissolved in 2 L of anhydrous dichloromethane containing 200 g of activated molecular sieves. 266 g of 8-

methoxycarbonyloctanol was charged to the reaction mixture along with 317 g of mercuric cyanide. The solution was stirred rapidly at room temperature for 24 hours. After checking for reaction completion by t.l.c. the reaction mixture was filtered through a buchner funnel of silica and the organic layer washed twice with water, twice with a 5% solution of potassium iodide and twice with a saturated solution of sodium bicarbonate. The solution was dried over sodium sulphate and evaporated to dryness. The residue was taken up in anhydrous methanol and treated with 1 g of freshly cut sodium then stirred at room temperature overnight. The solution of 8-methoxycarbonyloctyl 2-acetamido-2-deoxy-ß-D-glucopyranoside was neutralized with acid ion exchange resin and filtered and evaporated to yield 218 g of product after crystallization from isopropanol /diisopropyl ether.

Two hundred grams of 8-methoxycarbonyloctyl 2-acetamido-2-deoxy-ß-D-glucopyranoside was dissolved in 1.2 L of anhydrous dimethylformamide and treated with 169 mL of dimethoxytoluene (benzylaldehyde dimethyl acetal) and 1-2 g of p-toluenesulphonic acid. The reaction was stirred and heated to 40°C for 5 hours, then checked for completion by t.l.c. When the reaction appears complete the mixture was neutralized with triethylamine and quenched into several volumes of ice water, extracted into dichloromethane and backwashed several times with water. The organic layer was dried over sodium sulphate, evaporated to dryness and taken up in hot isopropanol. After cooling 8-methoxycarbonyloctyl-2-acetamido-4,6-O-benzylidene-2-deoxy-ß-D-glucopyranoside precipitates. It is filtered and dried to yield 106 g of product. ^{1}H-n.m.r. ($CDCl_3$): δ = 7.41 (m,5H, aromatic), 6.11 (d, 1H, NH),

5.5 (s, 1H, CH), 4.63 (d, 1H, H-1, $J_{1,2}$ 7.4 Hz), 2.29 (t, 2H), 1.99 (s, 3H, Ac), 1.58 (m, 4H), 1.29 (bs, 8H).

Example 4 -- Synthesis of 8-Methoxycarbonyloctyl 2-acetamido-3-O-p-methoxybenzyl-4,6-O-benzylidene-ß-D-glucopyranoside (compound 6).

To a stirred solution of compound 5 (17.5 g, ~3 mmol) in dry dichloromethane (100 mL) and catalytic amount of p-toluenesulfonic acid (0.25 to 3 weight percent based on compound 5) was added dropwise a solution of p-methoxybenzyl trichloroacetimide (10 g in 25 mL CH_2Cl_2). The reaction mixture was stirred at room temperature overnight. Triethylamine was added to quench the reaction, the organic layer was washed with sodium bicarbonate solution and the organic layer dried and evaporated to dryness, Crystallization in hot ethanol gave 20 g of the desired product. ^{1}H-n.m.r. ($CDCl_3$): δ 7.56-6.90 (m, 9H, aromatic), 5.60 (d, 1H, NH), 5.30 (s, 1H, PhCH), 4.94 (d, 1H, $J_{1,2}$ 8.0Hz, H-1), 3.80 (s, 3H, CH_3), 3.60 (s, 3H, CH_3Ph), 2.30 (t, 2H, CH_2CO), 1.90 (s, 3H, AcNH), 1.80-1.10 (m, 12H, $(CH_2)_6$).

Example 5 -- Synthesis of 8-Methoxycarbonyloctyl 2-acetamido-2-deoxy-3-O-p-methoxybenzyl-6-O-benzyl-2-ß-D-glucopyranoside (compound 7)

To a stirred solution of compound 6 (15.0 g, ~3 mmol) in 200 mL of dry THF were added, 11.0 g of sodium cyanoborohydride, 10 g of molecular sieves 4Å and 5 mg of methyl orange. The solution was cooled to -10°C and then ethereal hydrochloric acid was added dropwise until the solution remained acidic. On completion of the reaction, it was diluted with dichloromethane (200 mL), filtered through celite and washed successively

with aqueous sodium bicarbonate (2 x 100 mL) and water (2 x 100 mL) and then the solvent dried and evaporated to give a syrup. Purification of the mixture on column chromatography using silica gel as adsorbent and eluting with hexane:ethyl acetate:ethanol (20:10:1) gave 7 in 70% yield. ^{1}H-n.m.r. ($CDCl_3$): δ 7.40-6.90(m, 9H, aromatic), 5.70(d, 1H, NH), 4.64(d, 1H, $J_{1,2}$ 8.0Hz, H-1), 3.86(s, 3H, CH_3O), 3.68(s, 3H, CH_3OPh), 2.30(t, 2H, CH_2CO), 1.90(s, 3H, NHAc), 1.80-1.10(m, 12H, $(CH_2)_6$).

Example 6 -- Synthesis of 8-Methoxycarbonyloctyl 2-acetamido-2-deoxy-3-O-p-methoxybenzyl-4-O-(4,6-O-benzylidene-2,3-O-dibenzoyl-ß-D-galactopyranosyl)-6-O-benzyl-2-deoxy-ß-D-glucopyranoside (compound 42)

A solution of compound 7 (10.61 g, 19.7 mmol) and compound 32A (1.6-1.7 equivalents based on compound 7) and 2,6-di-t-butyl-4-methyl pyridine (3.11 g, 15.2 mmol) in 250 L of dichloromethane and 40 g of molecular sieves (4Å) was stirred at room temperature for 30 minutes, and then cooled to -50°C under nitrogen. A dry solution of silver triflate (4.47 g, 17.3 mmol) in toluene (40 mL) was added to the stirred mixture. The mixture was warmed to -15°C during two hours and kept at -15°C for an additional 5 hours. At the end of which the mixture was warmed to room temperature and stirred overnight. 3 mL of pyridine and 250 mL of dichloromethane were added to the mixture and was filtered over celite, filtrate was washed with saturated aqueous sodium hydrogen carbonate (200 mL) and then with water (200 mL), aqueous hydrogen chloride (0.5N, 200 mL) and water (200 mL), concentrated in vacuo. 6.0 g of compound 8 was crystallized as white crystals from ethyl acetate-diethyl ether-hexane. The

mother liquor was concentrated, purified over chromatography (300 g silica gel, toluene:ethyl acetate, (1:1) to give 4.5 g pure compound **42**. Total yield was 10.5 g (68%). Rf 0.48 (methanol:dichloromethane, 4:96). ^{1}H-n.m.r. ($CDCl_3$): δ 5.80(t, 1H, $J_{2',3'}$ 11.0Hz, H-2'), 5.52(s, 1H, CHPh), 5.25(dd, 1H, $J_{3,4}$ 4.0Hz, H-3'), 4.88(d, 1H, $J_{1',2'}$ 11.0Hz, H-1'), 4.70(d, 1H, $J_{1,2}$ 9.0Hz, H-1), 3.78(s, 2H, CH_3O), 3.64(s, 3H, CH_3OPh).

Example 7 -- Synthesis of 2-O-benzoyl-4,6-O-benzylidene-3-O-chloroacetyl-α-D-galactopyranosyl bromide (compound **33**)

Compound **32**, benzyl 4,6-O-benzylidene-2-O-benzoyl-3-chloroacetyl-β-D-thiogalactopyranoside (8.87 g) was dissolved in 100 mL of dichloromethane, cooled to 0°C and treated with a solution of bromine (2.7 g) in 10 mL of dichloromethane. After 15 minutes, 1.7 g of tetraethylammonium bromide was added to the mixture and the mixture stirred for 2 to 3 hours at room temperature (followed by t.l.c. on silica gel). A small quantity of cyclohexene was added to quench excess bromine and the reaction mixture was quenched into cold saturate sodium bicarbonate solution, washed with water, dried, and the volume of the solution reduced to 30 mL so as to provide a dichloromethane solution of compound **33**. This solution was used directly in the synthesis of compound **37**.

Example 8 -- Synthesis of 8-methoxycarbonyloctyl 2-acetamido-4-O-(2'-O-benzoyl-4',6'-O-benzylidene-3'-O-chloroacetyl-ß-D-galactopyranosyl)-6-O-benzyl-2-deoxy-3-O-p-methoxybenzyl-ß-D-gluco-pyranoside (compound 37)

A solution of the compound 7 (5.0 g, 0.9 mmol) and compound 33 (1.4 to 1.5 equivalents -- from example 7) and 2,6-di-t-butyl-4-methyl pyridine (1.78 g, 1.0 mmol) in 50 mL of dichloromethane and 20 g of molecular sieves (4Å) was stirred at room temperature for 30 minutes, and then cooled to -50°C under nitrogen. A dry solution of silver triflate (3.3 g, 1.5 mL) in toluene (10 mL) was added to the stirred mixture. The mixture was warmed to -15°C over two hours and kept at -15°C for an additional 5 hours, then allowed to warm to room temperature and stirred overnight. 1 mL of pyridine and 100 mL of dichloromethane were added to the mixture and it was filtered over celite, the filtrate was washed with aqueous sodium bicarbonate (100 mL) and then with water (100 mL), aqueous hydrogen chloride (0.5 N, 100 mL) and water (100 mL), then concentrated in vacuo. Purification of the crude mixture on column chromatography with silica gel as adsorbent eluted with hexane:ethyl acetate (1:1) gave 5.2 g of pure compound 37. ^{1}H-n.m.r. ($CDCl_3$): δ 5.85(d, 1h, NH), 5.62(t, 1H, $J_{2',3'}$ 10.8Hz, H-2'), 5.52(s, 1H-CH-benzylidene), 5.08 (dd, 1H, $J_{3',4'}$ 4Hz, H-3'), 4.85 (d, 1H, $J_{1',2'}$ 11.0Hz, H-1'), 4.68 (d, 1H, $J_{1,2}$ 9.0Hz, H-1), 3.72 and 3.64 (2s, 6H, $OC\underline{H}_3$ and $COOC\underline{H}_3$); ^{13}C-n.m.r.: 159.0(aromatic c-p-methoxyl) 165.15(c=0, chloroacetyl), 167.12(c-0, acetyl), 174.2(c=0, $\underline{C}OOCH_3$), 99.64(c-1), 100.26(c-1'), 101.0(PhC$\underline{H}$).

Example 9 -- Synthesis of 2-deoxy-2-phthalimido-1,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (compound 1)

(D+) Glucosamine hydrochloride (100 g, 0.46 mol) was added to a solution of sodium methoxide in methanol which was prepared from equimolar amount of sodium metal in methanol (0.5 L). The resultant mixture was treated with equimolar equivalent of phthalic anhydride and triethylamine (80 mL). The mixture was then stirred for 2 hours, filtered and the solid was dried in vacuum for 12 hours. The dry solid was dissolved in pyridine (300 mL) and treated with acetic anhydride (200 mL, 2.1 mol). The mixture was stirred at room temperature for 48 hours and then quenched in an ice-water mixture, and the resultant precipitate was filtered, concentrated and crystallized from diethylether to 98.3 g (45%) of the title compound. ^{1}H-n.m.r. ($CDCl_3$): δ 7.75 (m, 4h, aromatic), 6.45 (d, 1H, H-1, $J_{1,2}$ 9.0Hz), 5.85 (t, 1H), 5.15 (t, 1H), 4.4 (t, 1H), 4.3 (q, 1H), 4.1 (q, 1H), 4.00 (m, 1H), 2.05, 2.00, 1.95, 1.80 (4s, 12H, 4Ac). ^{13}C-n.m.r. ($CDCl_3$) δ 89.7 (C-1), 72.6, 70.5, 68.3 (3C, C-3, C-4, C-5), 61.45 (C-6), 53.42 (C-2).

Example 10 -- Synthesis of 2-deoxy-2-phthalamido-3,4,6-tri-O-acetyl-β-D-glucopyranosyl bromide (compound 12)

2-deoxy-2-phthalamido-1,3,4,6-tetra-O-acetyl-β-D-glucopyranoside 1 (20g, 41.9mmol) was treated with hydrogen bromide solution in acetic acid (30%, 200mL) and stirred at room temperature for 2 hrs. The mixture was then poured into an ice water mixture and extracted with dicloromethane. The extract was washed with $NaHCO_3$ solution and water followed by $MgSO_4$ drying. The mixture is filtered, dried and

concentrated in vacuo to give compound 12 as a dry syrup (compound 12)

Example 11 -- Synthesis of Ethyl 2-deoxy-2-phthalimido-3,4,6-tri-O-acetyl-β-D-glucopyranoside (compound 13)

2-Deoxy-2-phthalamido-3,4,6-tri-O-acetyl-β-D-glucopyranosyl bromide (compound 12) from example 16 was taken up in dry ethanol and treated directly with dry ethanol (200 mL), mercuric cyanide (13.7 g. 55 mmol) and stirred at room temperature for 48 hr. The mixture was then filtered and concentrated. The residue was taken up in 200 mL of dichloromethane and washed with a solution of 10% potassium iodide, 5% sodium bicarbonate, water, dried over $MgSO_4$ and concentrated to a syrup.

Example 12 -- Synthesis of Ethyl 2-deoxy-2-phthalimido-β-D-glucopyranoside (Compound 14)

Ethyl 2-deoxy-2-phthalamido-3,4,6-tri-O-acetyl-β-D-glucopyranosyide (compound 13) from example 17 was taken up in 100 mL of dry methanol and treated with 100 mg of sodium metal. The solution was stirred at room temperature for 24 hours and then neutralized with Amberlite [R-120(H+)] resin, filtered, and evaporated to dryness in vacuo. This compound was used in the preparation of compound 15 and compound 66.

Example 13 -- Synthesis of Ethyl 2-deoxy-2-phthalimido-6-O-benzyl-β-D-glucopyranoside (Compound 15)

Compound 14 (2.1 g, 6.23 mmol) was taken up in 100 mL of toluene. To it was added bis(tributyl tin) oxide (2.22 mL, 4.35 mmol) and tetrabutylammonium bromide (0.983 g, 3.05 mmol). The mixture was heated at 150°C for 4 hours and then toluene (50 mL) was distilled off from the mixture. The reaction mixture was cooled to room temperature and benzyl bromide (2.17 mL, 18.27 mmol) was added and the reaction heated to 110°C for 36 hours. Toluene was evaporated and the residue taken up in ethyl acetate (22 mL), washed successively with aqueous sodium bicarbonate, saturated sodium chloride solution and water. The organic layer was dried and evaporated to dryness to give a crude solid. Purification by column chromatography on silica gel gave a crystalline solid 15 (1.4 g, 70%). ^{1}H-n.m.r.($CDCl_3$) δ 7.3-8.1 (9H, aromatic), 4.5 (dd, 2H, $C\underline{H}_2Ph$), 5.18 (d, 1H, $J_{1,2}$ 10.0Hz, H-1), 4.36 (dd, 1H, H-3), 4.25 (dd, H, $J_{2,1}$ 10.0Hz, $J_{2,3}$ 8.0Hz, H-2) and 1.0(t, 3H, CH_3).

Example 14 -- Synthesis of Ethyl 2-acetamido-6-O-acetyl-3-O-benzyl-2-deoxy-β-D-glucopyranoside

A solution of compound 90 (described below-2 g, 4.68 mmol) in aqueous acetic acid (80%, 150 mL) was heated at 80°C for 2 hours. The mixture then was evaporated and the resultant solid was dried over P_2O_5 in high vacuum. The dry solid was selectively acetylated with acetyl chloride (0.33 mL, 4.7 mmol) and pyridine (10 mL) in dichloromethane (100 mL) at -10°C to 5°C. The mixture was then diluted with dichloromethane (50 mL), washed with aqueous $NaHCO_3$,

dried over $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column using EToAc: hexanes, 3:1 (v:v) as eluant to give 0.82 g (46%) of the title compound: ^{1}H-n.m.r. (300 MHz, $CDCl_3$) δ7.3(m, 5H, aromatic), 5.67(bs, 1H, NH), 4.86(d, 1H, H-1), 4.75(m, 2H), 4.48(q, 1H), 4.27(d, 1H), 4.1(t, 1H), 3.85(m, 1H), 3.5(m, 3H), 3.16(m, 1H), 2.70(bs, 1H, OH), 2.1(s, 3H, Ac), 1.9(s, 3H, Ac), 1.18(t, 3H, CH_3), ^{13}C-n.m.r. ($CDCl_3$): δ 99.45(C-1), 79.85, 74.5(CH_2ph), 73.7, 71.09, 65.25 (C-6), 63.36(CH_2-), 57.7(C-2), 23.6(Ac), 20.86(Ac), 15.06(CH_3).

Example 15 -- Synthesis of Ethyl 6-O-acetyl-3-O-benzyl-2-deoxy-2-phthalimido-ß-D-glucopyranoside (compound 69)

A solution of ethyl 2-deoxy-2-phthalimido-β-D-glucopyranoside (compound 14) from Example 12 was taken up in dry acetonitrile (100 mL) and treated with benzaldehyde dimethylacetal (9.6 g) and a catalytic amount of p-toluenesulphonic acid (100 mg). The mixture was stirred for 17 hours at room temperature and then neutralized to pH 7 with triethylamine. The mixture was evaporated and crystallized from hot hexanes to give 12.7 grams of ethyl 4,6-O-benzylidene-2-deoxy-2-phthalimido-ß-D-glucopyranoside compound 66.

Compound 66 (10 g) was dissolved in dry dimethylformamide (DMF) at -5°C and treated with 1.1 g (46.6 mol) sodium hydride and benzyl bromide (5.46 mL, 22 mmol). The mixture was stirred at 0°C for 2 hours and then treated slowly with 20 mL methanol then slowly brought to room temperature and treated with HCl (1N) to pH 7 and then extracted three times with dichloromethane. The organic layer was dried over anhydrous magnesium sulfate then filtered, concentrated to dryness and taken up in hot ethanol to give 7.2 g of

compound 67. Compound 67 (5.43 g, 10.50 mmol) in aqueous acetic acid (80%, 200 mL) was heated at 80°C for 2 hours. The mixture was evaporated and the resultant solid was dried over P_2O_5 in high vacuum. The dry solid was selectively acetylated with acetyl chloride (0.8 mL, 11.0 mmol) and pyridine (10 mL) in dichloromethane (200 mL) at -10°C to 0°C. The mixture was then diluted with dichloromethane (1 0 mL), washed with aqueous $NaHCO_3$, dried over $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column using EtOAc:hexane, 1:2 (v:v) as eluant to give 3.5 g (71%) of the compound 69: ^{1}H-n.m.r. (300 MHz, $CDCl_3$): δ 7.7(m, 4H, aromatic), 7.0(m, 5H, aromatic), 5.16(d, 1H, H-1), 4.7(d, 1H), 4.5(m, 2H), 4.2(m, 3H), 3.8(m, 1H), 3.6(m, 2H), 3.45(m, 1H), 2.9(bs, 1H, OH), 2.1(s, 3H, Ac), 1.95(t, 3H, CH_3). ^{13}C-n.m.r. ($CDCl_3$): δ 98.09(C-1), 78.45, 74:5, 73.9, 71.7, 65.1, 63.1, 55.5, 20.87 (Ac), 14.92 (CH_3).

Example 16 -- Synthesis of Ethyl 6-O-acetyl-3-benzyl-2-deoxy-2-phthalimido-4-O-(2,3,4,6-tetra-O-acetyl-ß-D-galactosyl)-ß-D-glucopyranoside (compound 70)

To a stirred solution of compound 9 (80 mg, 0.17 mmol) in dichloromethane (10 mL) containing molecular sieves (3A°, 1 g), 2,6-di-tert-butyl-4-methyl-pyridine (45 mg, 0.22 mmol) and silver triflate (57 mg, 0.22 mmol) was added, at -30°C under nitrogen, 2,3,4,6-tetra-O-acetyl-α-D-galactosyl bromide in dichloromethane (5 mL). The mixture was stirred at this temperature for 1 h and then warmed up to 5°C over 2h. The mixture was then diluted with dichloromethane (10 mL), filtered and the insoluble material was washed with dichloromethane (5 mL). The combined filtrates were washed with saturated aqueous sodium hydrogen

carbonate and water, dried over $MgSO_4$, and concentrated. The residue was chromatographed on a silica gel column using ethyl acetate: hexanes, 1:2 (v:v) as eluant to give 120 mg (80%) of the title compound: ^{1}H-n.m.r. (300 MHz, $CDCl_3$): δ 7.68, 6.96(2m, 9H, aromatic), 5.3(m, 2H), 5.13(d, 1H, H-1', $J_{1',2}$ 8.0Hz), 4.99(q, 1H), 4.82(d, 1H), 4.62(d, 1H, H-1, $J_{1,2}$ 7.7Hz), 4.54(d, 1H), 4.42(d, 1H), 4.3(q, 1H), 4.15(m ,2H), 3.99(m, 2H), 3.87(m, 2H), 3.72(m, 2H), 3.46(m, 1h), 2.15, 2.12, 2.09, 2.00, 1.98(5s, 15H, 5XAc), 1.00(t, 3H, CH_3).
^{13}C-n.m.r. ($CDCl_3$): δ 101.2, 97.8(C-1, C-1'), 14.85(CH_3).

In the following examples, unless indicated otherwise, R = $-(CH_2)_8CO_2CH_3$

Example 17 -- Synthesis of 8-Methoxycarbonyloctyl 3-O-(4,6-O-benzylidene-3-O-sulfo-β-D-galactopyranosyl)-2-acetamido-4,6-O-benzylidene-2-deoxy-β-D-glucopyranoside (compound 105)

The title compound was prepared by first generating 8-methoxycarbonyloctyl 3-O-(2,3-di-O-benzoyl-4,6-O-benzylidene-β-D-galactopyrnosyl)-2-acetamido-4,6-O-benzylidene-2-deoxy-β-D-glucopyranoside which, in turn, was generated by coupling the 8-methoxycarbonyloctyl 2-acetamido-4,6-O-benzylidene-2-deoxy-β-D-glucopyranoside and compound 32, the synthesis of which is exemplified in example 2 above. The 8-methoxycarbonyloctyl 2-acetamido-4,6-O-benzylidene-2-deoxy-β-D-glucopyranoside can be prepared by reacting N-acetylglucosamine-OR (e.g., compound 4 in Figure 1) with about 1.5 equivalents of $C_6H_5CH(OCH_3)_2$ in an acidic (p-toluene sulfonic acid) acetonitrile or

dimethylformamide (DMF) medium at from about 0° to about 50°C over 6-48 hours to provide for the 4,6-O-protected benzylidine compound.

Coupling of compound 32 with the 8-methoxycarbonyloctyl 2-acetamido-4,6-O-benzylidine-2-deoxy-β-D-glucopyranoside ("compound A") can be achieved by first combining about 1 equivalent of N-iodosuccinimide with about 1 equivalent of trifluoromethanesulfonic acid in methylene chloride containing molecular sieves which remove any water present. The reaction mixture is cooled to -50°C and then compound A is added followed by the addition of approximately, 1 to 1.1 equivalents of compound 32 (based on compound A). When large amounts of trifluoromethanesulfonic acid are employed, the reaction is preferably cooled to -50°C prior to the addition of the trifluoromethanesulfonic acid.

The reaction is allowed to equilibrate to about -20° to 0°C over about 1-3 hours. The reaction solution is then quenched by cooling to -50° followed by the addition of triethylamine until neutral pH is reached. The solution is filtered through Celite and then washed with a saturated sodium bicarbonate solution and water. The organic layer was dried and stripped in vacuo to provide for 8-methoxycarbonyloctyl 3-O-(2,3-di-O-benzoyl-4,6-O-benzylidene-β-D-galactopyranosyl)-2-acetamido-4,6-O-benzylidine-2-deoxy-β-D-glucopyranoside ("compound B").

The benzoyl groups on compound B can be removed under Zemplen conditions (NaOMe/MeOH) to provide for 8-methoxycarbonyloctyl 3-O-(4,6-O-

benzylidene-β-D-galactopyranosyl)-2-acetamido-4,6-O-benzylidene-2-deoxy-β-D-glucopyranoside ("compound C").

Compound C (1 gram, 1.37 mmol) was dissolved in dry dimethylformamide (5.0 mL) and sulfur trioxide-pyridine complex (267.1 mg, 1.64 mmol) was added at -30°C. The resulting solution was stirred at -30°C for 5 hours and then 15 hours at 0°C. Excess reagent was destroyed by the addition of methanol (2 mL). The The reaction mixture was converted into sodium salt by passage through Dowex 50-X8 (Na+) resin in methanol. Evaporation and co-evaporation with toluene left a while solid which was purified by chromatography on silica gel using dichloromethane-methanol-pyridine (9:1:0.1) as eluant to provide the title compound as a white solid. This material was converted into sodium salt by passage through Dowex 50-X8 (Na+) resin in methanol to give the title compound (850 mg, 74.6%).

Example 18 -- Synthesis of 8-Methoxycarbonyloctyl 3-O-(3-O-sulfo-β-D-galactopyranosyl)-2-acetamido-2-deoxy-β-D-glucopyranoside

The product of Example 17 (800 mg, 0.96 mmol) was dissolved in methanol (10 mL) containing 5% palladium on carbon (800 mg) and was stirred under hydrogen (1 atmosphere) for 5 hours at room temperature. Catalyst was removed by filtration, washed with methanol (500 mL) and the solvent was evaporated to dryness. The residue was then purified by chromatography on silica gel using dichloromethane-methanol-water-pyridine (80:20:2:0.2) as eluant. The title compound (488 mg, 77.5%) was obtained as a white solid after BioGel P-2 (200-400 mesh) filtration and conversion into its sodium salt. 1H.n.m.r. (D_2O)

δ: 4.520-4.570 [m, 2h, incl. H-1(d, 4.550, $J_{1,2}$ 8.0Hz and H1'(d, 4.542, $J_{1',2'}$ 7.7 Hz)], 4.277-4.343 [m, 2H, incl. H-3'(dd, 4.310, $J_{2,3}$ 10.0Hz, $J_{3,4}$ 3.5Hz) and H-4'(4.296)], 3.687(s, 3H, OCH_3), 2.388(t, 2H, J7.5Hz, CH_2COO),2.025(s, 3H, NHAc), 1.570(m,4H) and 1.30(m, 8H).

The 2,3-disulfate of Example 18 was prepared in a similar manner except that sulfation was conducted with 6 equivalents of sulfur trioxide/pyridine complex and the reaction was conducted at room temperature for 24 hours. The resulting product was a mixture of 2-, 3-sulfate and predominantly 2,3-disulfate. The mixture was purified by chromatography in the manner described and ion exchange of the resulting product provided for the 2,3-disulfate of Lewis^c-OR as the disodium salt.

The 2-sulfate of Lewis^c-OR was prepared from compound C by benzoylation under conditions described above. The resulting product contained predominantly the 3-benzoyl group on the galactose unit and a small amount of the 2-benzoyl and 2,3-dibenzoyl derivatives. The products were separated by chromatography on silica gel to provide for both the 2-benzoyl and the 3-benzoyl derivatives as pure products.

The 3-benzoyl derivative was sulfated in the manner described above and then deprotected to provide for the 2'-sulfo-Lewis^c-OR which upon ion exchange as described above provided for the sodium salt of this product.

The 3'-sulfo-LacNAc derivative was prepared from compound 42 (prepared in Example 6) wherein the dibenzoyl groups are removed via Zemplen conditions

(sodium methoxide/methanol) and then sulfated under the conditions described above to provide for 3'-sulfo-Lewis^c-OR.

The following Examples 19-20 illustrate the immunomodulating properties of the compounds of this invention.

Example 19 - Inhibition of DTH Inflammatory Response

DTH inflammatory responses were measured using the mouse footpad swelling assay as described by Smith and Ziola[14]. Briefly, groups of Balb/c mice were immunized with 100 μg of the OVA antigen [Albumin, chicken egg, Sigma, St. Louis, Missouri] containing 20μg of the DDA adjuvant (dimethyldioctadecylammonium bromide) which has been shown to induce a strong inflammatory DTH response. Seven days later, each group of mice was footpad-challenged with 20 μg of OVA antigen. The resulting inflammatory footpad swelling was measured with a Mitutoyo Engineering micrometer 24 hours after challenge.

To assess the effect of the analogues of Lewis^c-OR and LacNAc-OR on the inflammatory DTH response, groups of mice received 100 μg of the following oligosaccharide glycosides 5 hours after foot-pad challenge with the OVA antigen.

Compound A = 3'-Sulfo-Lewis^c-OR
[3'-sulfo-βGal(1-3)βGlcNAc-OR]

Compound B = 2'-Sulfo-Lewis^c-OR
[2'-sulfo-βGal(1-3)βGlcNAc-OR]

Compound C = Sialyl Lewis^{X}-OR
[αNeu5Ac(2→3)βGal(1-4)-[α-L-Fuc(1-3)]-
βGlcNAc-OR]

Compound D = Sialyl Lewis^{A}-OR (αNeu5Ac(2→3)βGal(1-3)-
[α-L-Fuc(1-4)]-βGlcNAc-OR]

Compound E = Sialyl Lewis^{c}-OR
[αNeu5Ac(2→3)βGal(1-3)-βGlcNAc-OR]

Percentage reduction in inflammation for this example was calculated by the following equation:

$$100 - 100 \times \left[\frac{\text{Swelling of Treated Mice -bkg swelling}}{\text{Swelling of Untreated Mice - bkg swelling}}\right]$$

"Treated mice" are those mice which receive one of the above compounds in addition to the antigen. "Untreated Mice" are those mice which do not receive any of the above compounds. Background (bkg) swelling is that level of swelling observed in mice immunized with PBS alone without antigen or compound and challenged with antigen.

The results of this experiment are set forth below:

Compound	% Reduction in Inflammation
A	~59%
B	~35%
C	~24%
D	~30%
E	~41%

In a separate study, 3'-sulfo-LacNAc was shown to reduce inflammation by about 24% when administered to OVA sensitized mice 5 hours after OVA challenge in the manner described above.

The above results demonstrate that the compounds of this invention are effective in treating mammalian cell mediated secondary immune responses arising from antigen challenge.

Example 21 -- Effect of Oligosaccharide Glycosides on LPS Caused Lung Injury

LPS (lipopolysaccharide) caused lung injury is measured by weighing the lungs of sacrificed mice 24 hours after mice are given LPS intranasally. Briefly, groups of 8-10 week old Balb/c mice were sensitized with 5 μg /mouse of LPS in 50 μl of PBS intranasally under light anesthesia.

The method of administering compound intranasally is described in Smith et al.[15], which is incorporated by reference. Briefly, mice are anethesitized with Metofane (Pitman-Moore Ltd., Mississauga, Ontario, Canada) and a 50 μl drop of compound is placed on the nares of the mouse and is inhaled.

Five hours later, 100 μg/mouse of 3'-sulfo-Lewis^c-OR in 200 μl of PBS is given to the mouse intravenously. After 24 hours, 48 hours or 72 hours, different groups of mice are sacrificed and the lungs removed and weighed. The weight of the lungs of mice treated with 3-sulfo-Lewis^c-OR are compared against control (i.e., mice treated with LPS but to which 3-sulfo-Lewis^c-OR has not been administered). The percent reduction is measured by subtracting from 100 the following:

The fraction derived by a numerator whose value is the weight of the treated lungs subtracted from the weight of normal lungs (lungs from mice not exposed to LPS, 3-sulfo-Lewis^c-OR), and whose denominator whose value is the weight of the control lungs (mice that received only LPS) subtracted from the weight of normal lungs and multiplying the resulting fraction by 100.

The greater the percent reduction, the better the compound is in allevating lung damage.

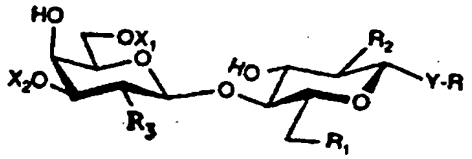
The results of this test are set forth below:

Time	% Reduction in Inflammation
24 hours	~53%
48 hours	~27%
72 hours	~52%

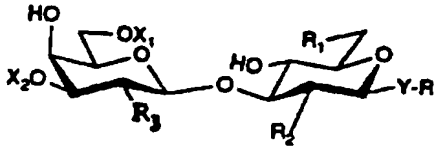
The above data demonstrates that the compounds of this invention are effective in reducing cell-mediated inflammatory responses due to injury.

WHAT IS CLAIMED IS:

1. A compound of Formula I or II:



I



II

where R is selected from the group consisting of hydrogen, a saccharide-OR_{19}, an oligosaccharide-OR_{19} having from 2 to 7 oligosaccharide units, or an aglycon having at least 1 carbon atom where R_{19} is hydrogen or an aglycon of at least one carbon atom;

Y is selected from the group consisting of oxygen, sulfur, and -NH-;

R_1 is selected from the group consisting of hydrogen, $-NH_2$, $-N_3$, $-NHSO_3H$, $-NR_5C(O)R_4$, $-N=C(R_5)_2$, $-NHCH(R_5)_2$, $-NHR_6$, $-N(R_6)_2$, -OH, $-OR_6$, $-S(O)R_6$, $-S(O)_2R_6$ and sulfate,

wherein R_4 is selected from the group consisting of

hydrogen,

alkyl of from 1 to 4 carbon atoms;

$-OR_7$ wherein R_7 is alkyl of from 1 to 4 carbon atoms, or alkyl of from 2 to 4 carbon atoms substituted with a hydroxyl group, and

$-NR_8R_9$ wherein R_8 and R_9 are independently selected from the group consisting of hydrogen and alkyl of from 1 to 4 carbon atoms,

each R_5 is selected from the group consisting of hydrogen and alkyl of from 1 to 4 carbon atoms,

each R_6 is alkyl of from 1 to 4 carbon atoms,

R_2 is selected from the group consisting of hydrogen, $-N_3$, $-NH_2$, $-NHSO_3H$, $-NR_{11}C(O)R_{10}$, $-N=C(R_{11})_2$, $-NHCH(R_{11})_2$, $-NHR_{12}$, $-N(R_{12})_2$, $-OH$ and $-OR_{12}$,

wherein R_{10} is selected from the group consisting of

hydrogen,

alkyl of from 1 to 4 carbon atoms,

$-OR_{13}$ wherein R_{13} is alkyl of from 1 to 4 carbon atoms, or alkyl of from 2 to 4 carbon atoms substituted with a hydroxyl group, and

$-NR_{14}R_{15}$ wherein R_{14} and R_{15} are independently selected from the group consisting of hydrogen and alkyl of from 1 to 4 carbon atoms,

each R_{11} is selected from the group consisting of hydrogen and alkyl of from 1 to 4 carbon atoms;

each R_{12} is alkyl of from 1 to 4 carbon atoms,

R_3 is selected from the group consisting of hydrogen, fluoro, sulfate and hydroxy;

X_1 is selected from the group consisting of hydrogen, sialyl, sulfate, phosphate, and $-CHR_{18}COOH$ where R_{18} is selected from the group consisting of hydrogen, alkyl of from 1 to 7 carbon atoms and -COOH;

X_2 is selected from the group consisting of hydrogen, sulfate, phosphate, and $-CHR_{18}COOH$ where R_{18} is selected from the group consisting of hydrogen, alkyl of from 1 to 7 carbon atoms and -COOH; and

pharmaceutically acceptable salts thereof;

and with the proviso that either at least one of X_1 or X_2 is sulfate, phosphate or $-CHR_{18}COOH$ or R_3 is sulfate.

2. A compound of Claim 1 wherein said compound is of Formula I.

3. A compound of Claim 1 wherein said compound is of Formula II.

4. A compound of Claim 1 wherein R_1 is selected from the group consisting of hydroxyl, hydrogen or alkoxy of from 1 to 4 carbon atoms.

5. A compound of Claim 1 wherein R_2 is selected from the group consisting of hydroxyl, alkoxy of from 1 to 4 carbon atoms, $-NH_2$, $-N_3$ and $-NHC(O)R_{10}$.

6. A compound of Claim 1 wherein R_3 is -OH.

7. A compound of Claim 1 wherein X and X_1 are hydrogen and X_2 is selected from the group consisting of sulfate, phosphate, and $-CHR_{18}COOH$.

8. A compound of Claim 1 wherein X and X_2 are hydrogen and X_1 is selected from the group consisting of sulfate, phosphate, and $-CHR_{18}COOH$.

9. A compound of Claim 2 wherein X_1 is hydrogen, X_2 is sulfate, R_1 is hydroxyl, R_2 is selected from the group consisting of $-NH_2$ and $-NHC(O)CH_3$ and R_3 is hydroxyl.

10. A compound of Claim 3 wherein X_1 is hydrogen, X_2 is sulfate, R_1 is hydroxyl, R_2 is selected from the group consisting of $-NH_2$ and $-NHC(O)CH_3$ and R_3 is hydroxyl.

11. A pharmaceutical composition suitable for administration to a mammal which comprises a pharmaceutically inert carrier and an effective amount of the compound of Claim 1 to modulate a cell-mediated immune response in said mammal.

12. A method for modulating a cell-mediated immune response in a mammal which method comprises administering to said mammal an amount of a compound of Claim 1 effective in modulating said immune response.

13. A method for reducing sensitization of a mammal to an antigen which comprises administration of an effective amount to the mammal of a compound of Claim 1.

14. A method for reducing sensitization of a mammal to an antigen which comprises administration of an effective amount to the mammal of a compound of Claim 2.

15. A method for reducing sensitization of a mammal to an antigen which comprises administration of an effective amount to the mammal of a compound of Claim 3.

16. A method according to Claim 12 wherein said suppression of an immune response comprises suppression of a DTH response and induction of tolerance to an antigen.

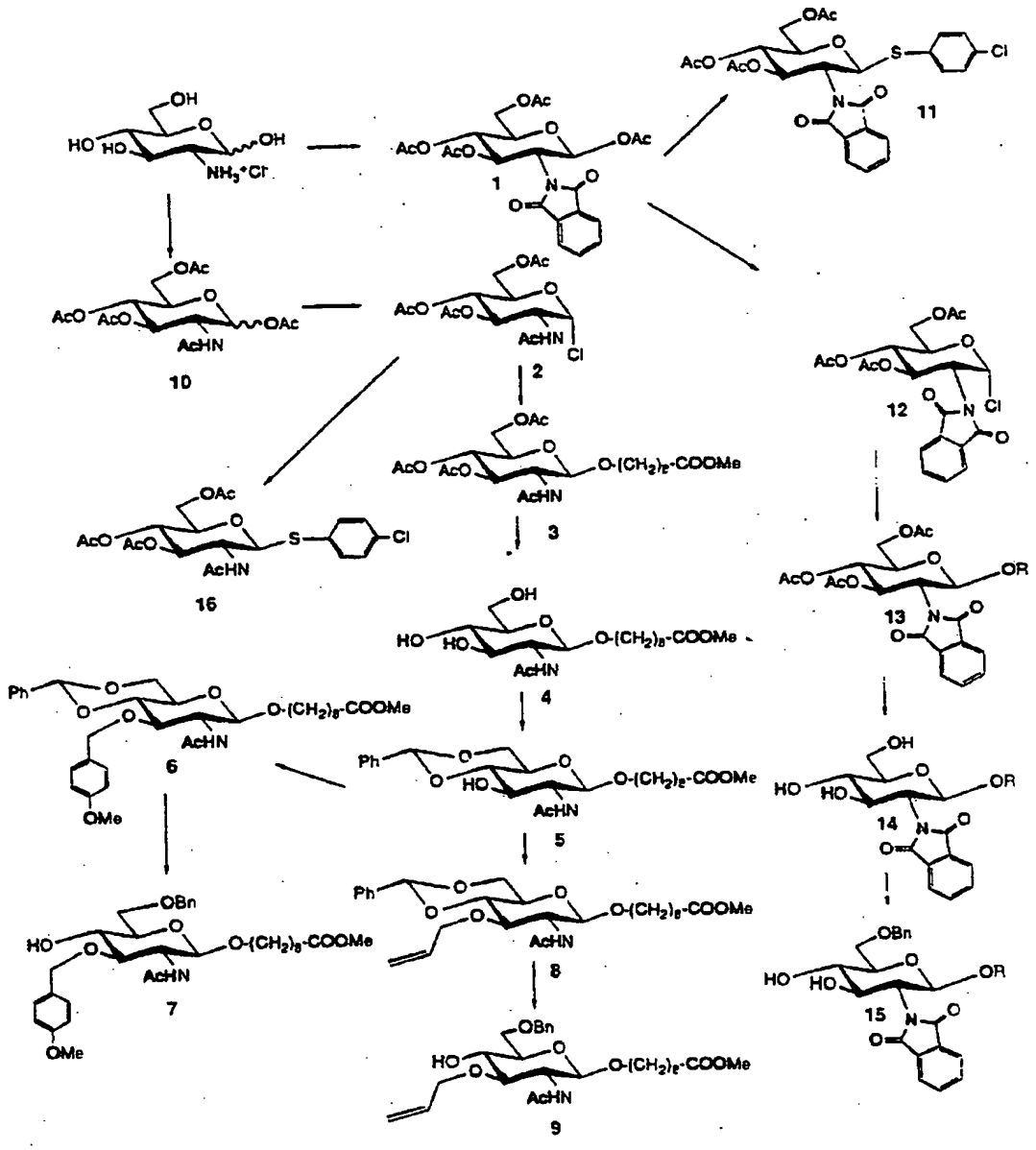


FIGURE 1

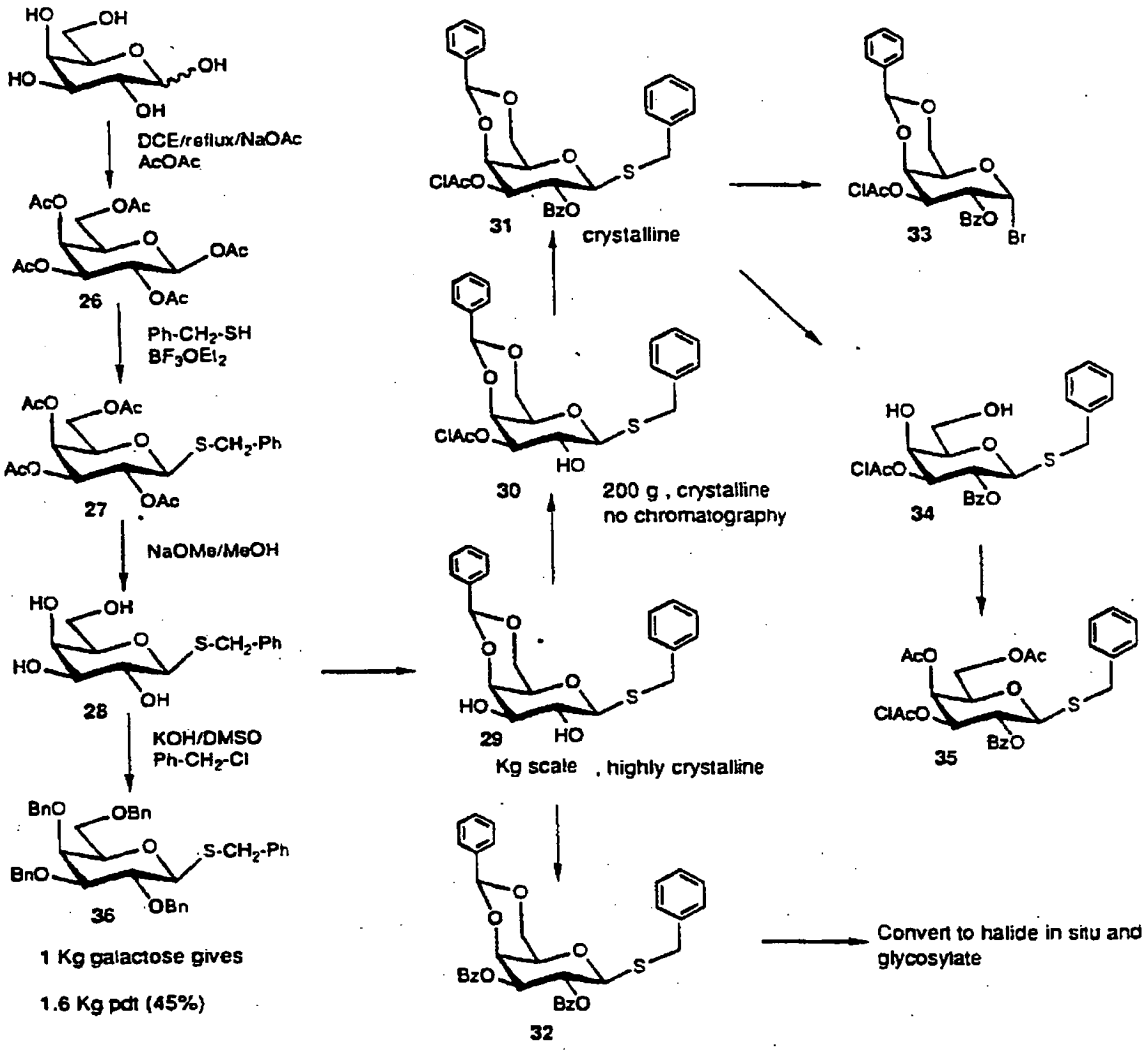


FIGURE 2

SUBSTITUTE SHEET

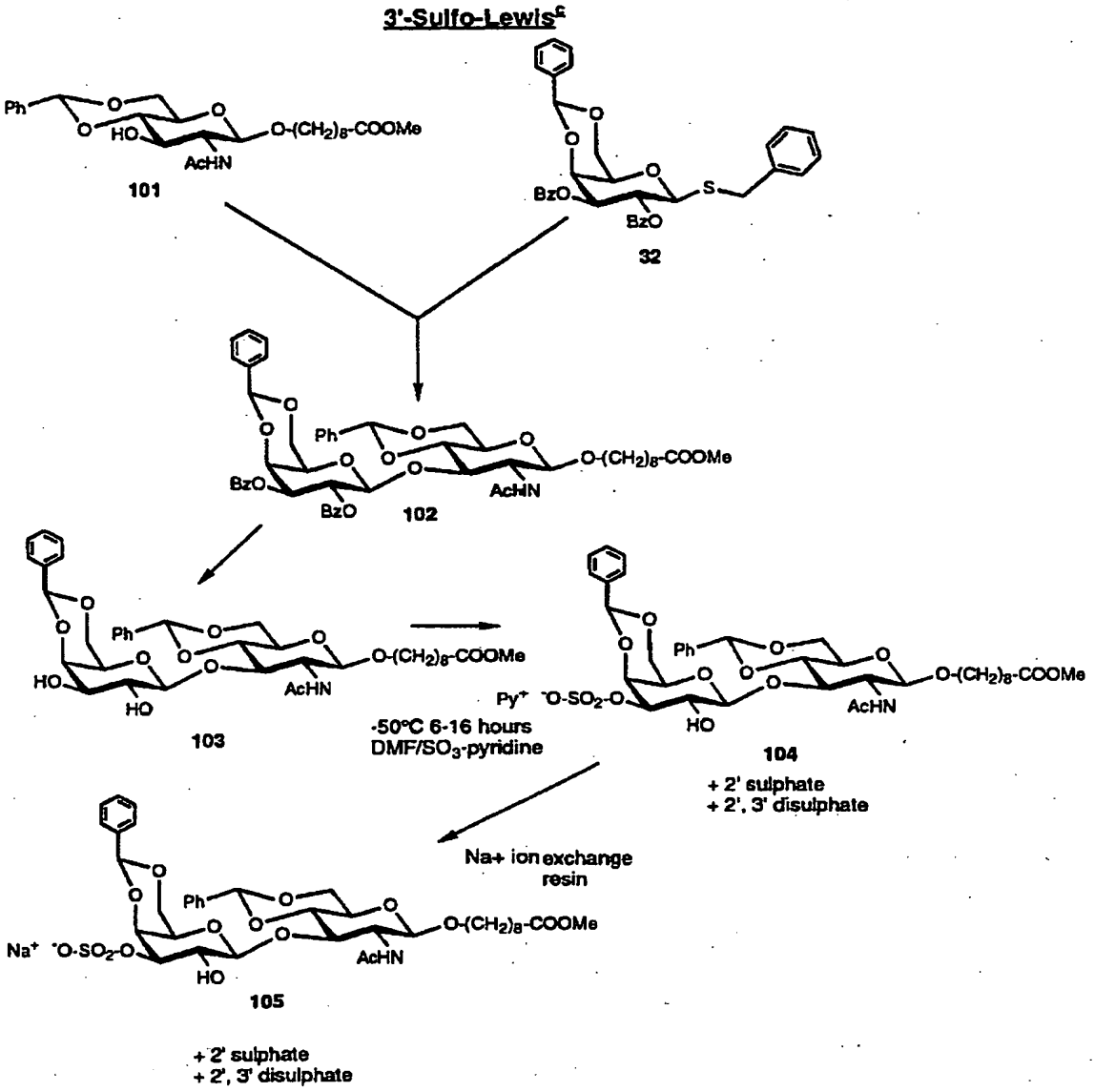

3'-Sulfo-Lewis^c
101
32
102
103
-50°C 6-16 hours
DMF/SO3-pyridine
104
+ 2' sulphate
+ 2', 3' disulphate
Na+ ion exchange resin
105
+ 2' sulphate
+ 2', 3' disulphate

FIGURE 3A

6'-sulfo Lewis c

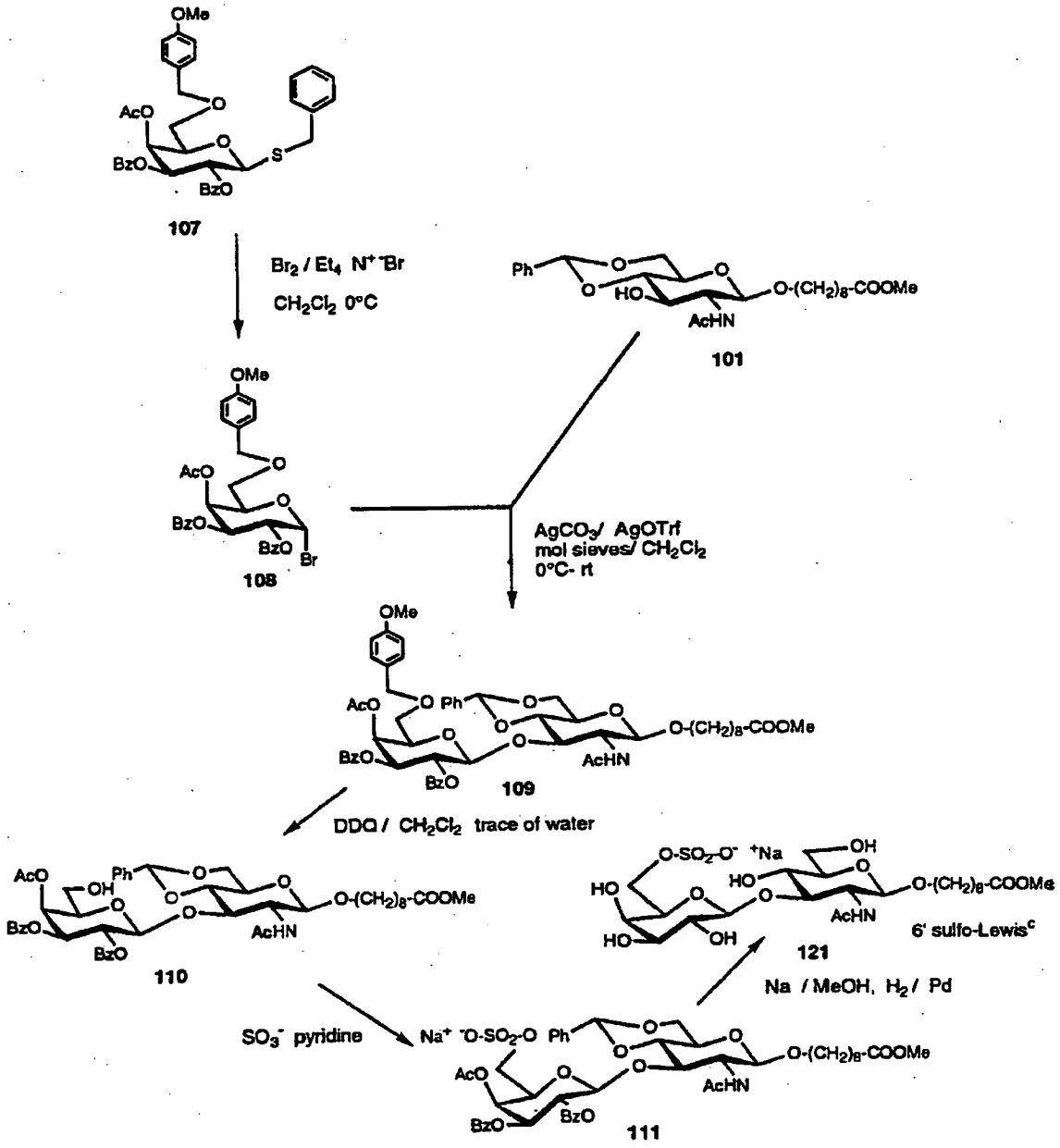


FIGURE 3B

SUBSTITUTE SHEET

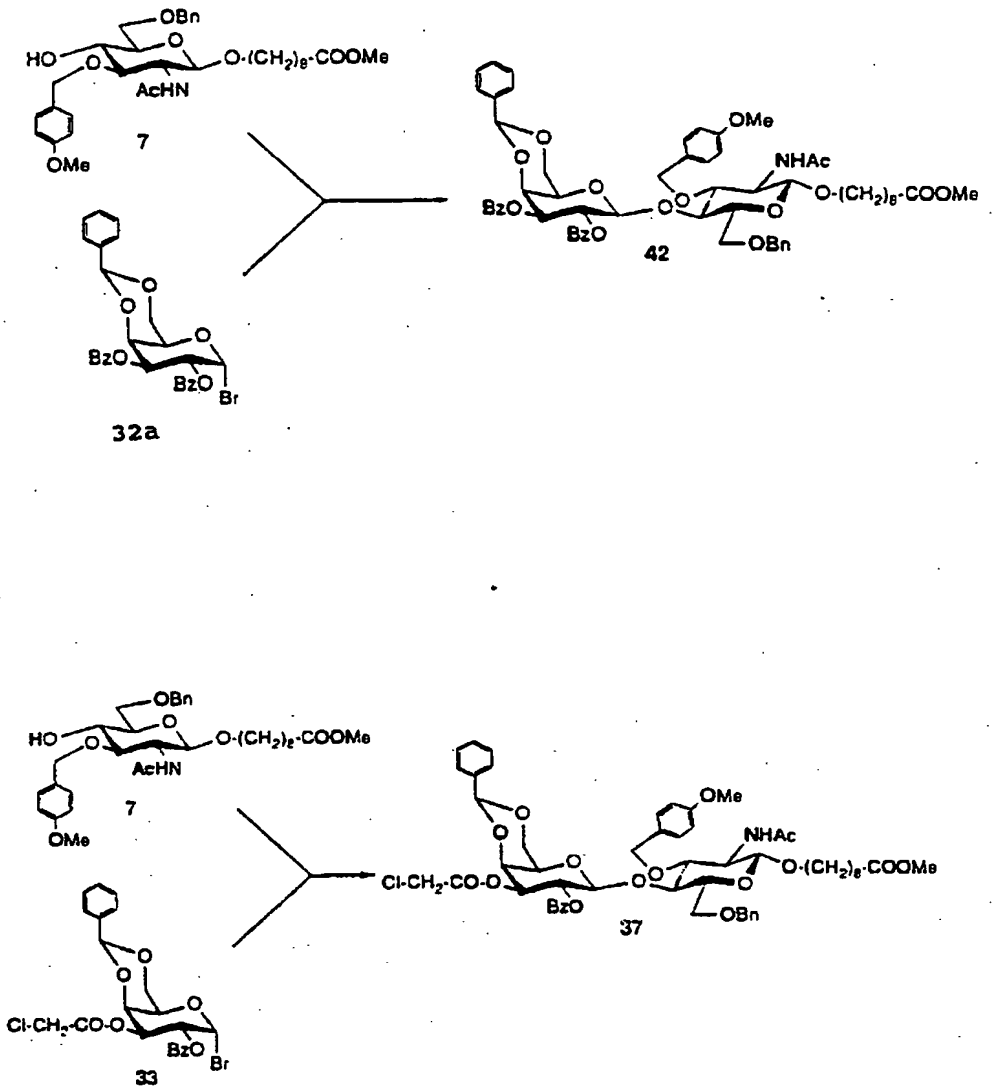

OBn
HO
O-(CH2)8-COOMe
AcHN
7
OMe
BzO
BzO
Br
32a
OMe
NHAc
O-(CH2)8-COOMe
BzO
BzO
OBn
42
Cl-CH2-CO-O
Cl-CH2-CO-O
BzO
Br
33
BzO
OBn
37

FIGURE 4

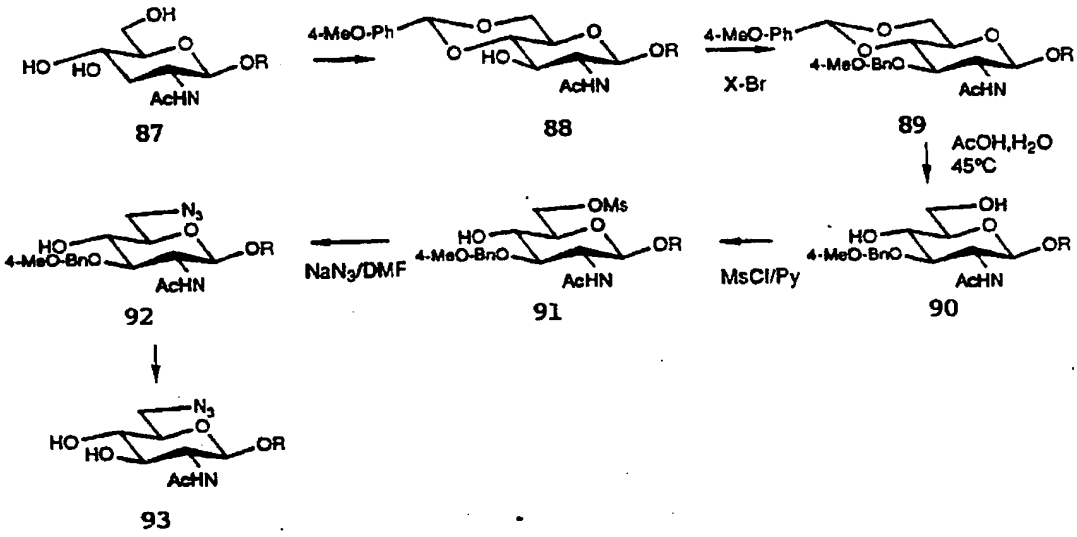

OH
HO
HO
O
OR
AcHN
87
4-MeO-Ph
O
O
HO
OR
AcHN
88
4-MeO-Ph
X-Br
O
O
4-MeO-BnO
OR
AcHN
89
AcOH,H2O
45°C
OH
HO
O
4-MeO-BnO
OR
AcHN
90
MsCl/Py
OMs
HO
O
4-MeO-BnO
OR
AcHN
91
NaN3/DMF
N3
HO
O
4-MeO-BnO
OR
AcHN
92
N3
HO
HO
O
OR
AcHN
93

FIGURE 5

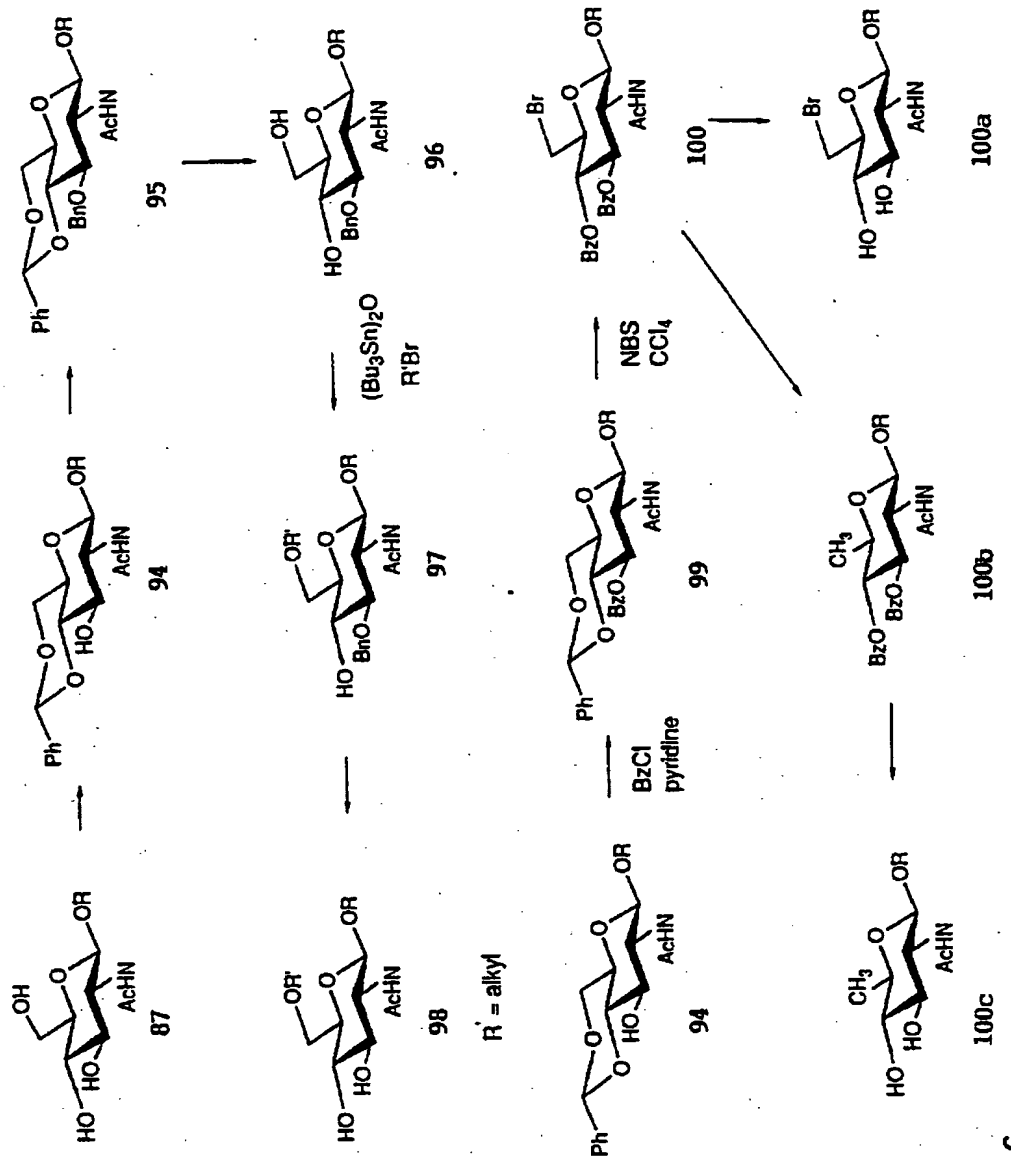

87
94
95
96
97
98
99
100
100a
100b
100c
R' = alkyl
(Bu3Sn)2O
R'Br
NBS
CCl4
BzCl
pyridine

FIGURE 6

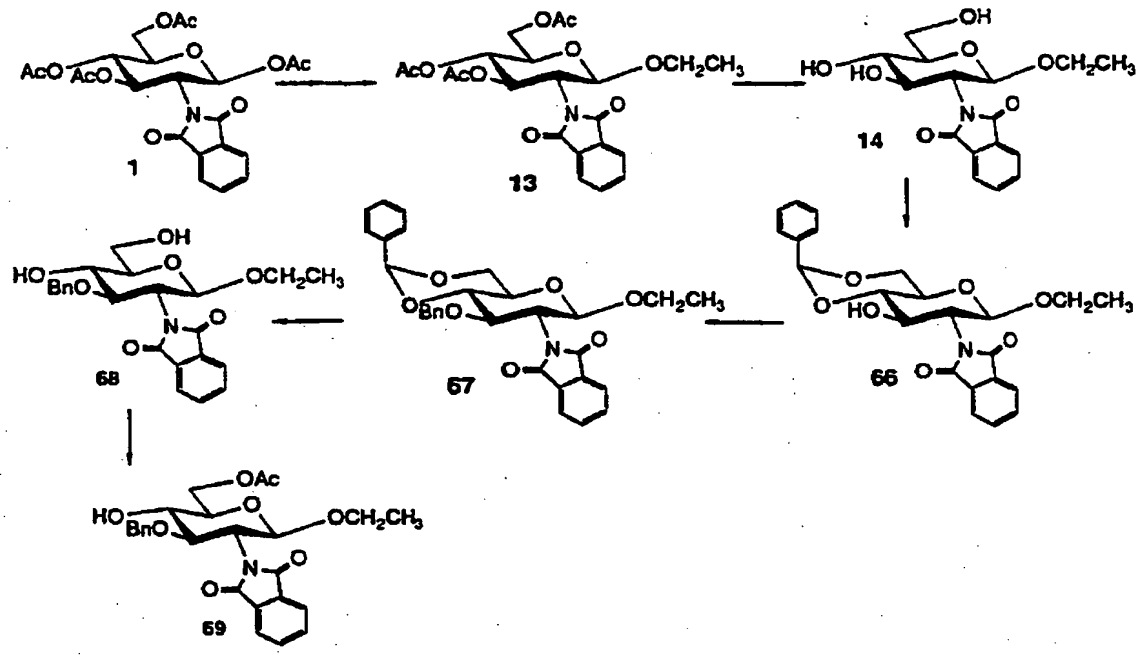


FIGURE 7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/04995

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :C07H 15/06, 1/00, 17/00; A61K 31/70
US CL :514/54, 53, 49; 536/53, 55.1, 18.7, 18.2, 4.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/54, 53, 49; 536/53, 55.1, 18.7, 18.2, 4.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

none

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS: Lacnac compounds, Lewis compounds, immunosuppressive, pharmaceutical

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A 5,079,353 (Ratcliffe et al) 07 January 1992, see entire document	1-14
Y	US, A 5,079,235 (Purifoy et al) 07 January 1992, see entire document	1-14

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 04 September 1993	Date of mailing of the international search report 14 SEP 1993
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. NOT APPLICABLE	Authorized officer MICHAEL G. WITYSHYN Telephone No. (703) 308-0196

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